(12) UK Patent Application (19) GB (11) 2 283 745 (13) A

(43) Date of A Publication 17.05.1995

(21) Application No 9422158.7

(22) Date of Filing 03.11.1994

(30) Priority Data
(31) 152620 (32) 12.11.1993 (33) US

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(74) continued overleaf

(51) INT CL[6]
C07D 209/26 , A61K 31/405

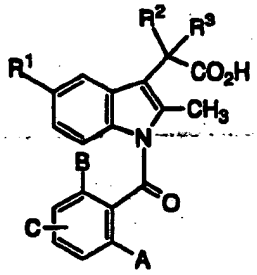
(52) UK CL (Edition N)
C2C CAA CLZ CMA CMC CMM CQS CQT CUH C1343 C213 C22Y C220 C25Y C250 C251 C30Y C31Y C311 C313 C314 C315 C32Y C323 C324 C326 C332 C337 C338 C35X C351 C355 C36Y C364 C366 C367 C37Y C373 C387 C389 C396 C397 C464 C490 C613 C614 C62Y C620 C621 C624 C625 C628 C634 C644 C658 C662 C665 C666 C669 C670 C672 C675 C694 C695 C697 C698 C712 C80Y C802
U1S S2416 S2417

(56) Documents Cited
Chemical Abstracts 106:50037 and JP610148160 A2

(58) Field of Search
UK CL (Edition M) C2C CUH
INT CL[5] C07D 209/26
Online databases: CAS ONLINE

(54) Pharmaceutically active N-acylindoles

(57) Compounds of the structure shown below and pharmaceutically acceptable salts thereof are specific inhibitors of cyclooxygenase-2 useful in the treatment of cyclooxygenase-2 mediated disease states such as inflammation, pain and fever, and are non-ulcerogenic:



R^1 is $-OCH_3$, $-N(CH_3)_2$, $-SCH_3$, $-OCF_3$, halo or lower alkyl;

R^2 and R^3 are independently H or lower alkyl or R^2 and R^3 may be joined to form a saturated hydrocarbon ring of 3 to 7 members;

A is halogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, CF_3, CN, N_3, NO_2, SCF_3 or OCF_3;

B is A or also H if A is CF_3;

C is A or H with the proviso that if A is CF_3, B and C are not both H;

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TITLE OF THE INVENTION

N-ACYLINDOLES AND RELATED COMPOUNDS

BACKGROUND OF THE INVENTION

This invention relates to novel N-acylindoles and related compounds; to methods of treating cyclooxygenase mediated diseases with the novel compounds; and to certain pharmaceutical compositions therefor.

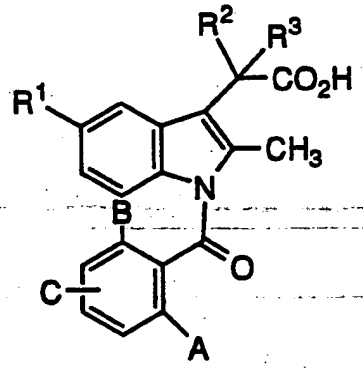
Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 (COX-1) or the constitutive enzyme, as originally identified in bovine seminal vesicles. More recently the gene for a second inducible form of cyclooxygenase (cyclooxygenase-2) (COX-2) has been cloned, sequenced and characterized initially from chicken, murine and human sources. This enzyme is distinct from the cyclooxygenase-1 which has been cloned, sequenced and characterized from various sources including the sheep, the mouse and man. The second form of cyclooxygenase, cyclooxygenase-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the constitutive enzyme, cyclooxygenase-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, cyclooxygenase-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of cyclooxygenase-2 will have similar antiinflammatory, antipyretic and analgesic properties

to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions, have potential anti-cancer effects and be useful in the treatment of Alzheimer's disease, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

U.S. Patents 3,161,654, 3,647,858 and 3,654,349 disclose compounds similar to those of the present invention. It has now been unexpectedly found that compounds with a substituent A in structure I fixed in the ortho position of the phenyl group attached to Y exhibit marked selectivity for the inhibition of Cox-2 over Cox-1.

SUMMARY OF THE INVENTION

This invention relates to the novel compound of Formula I.

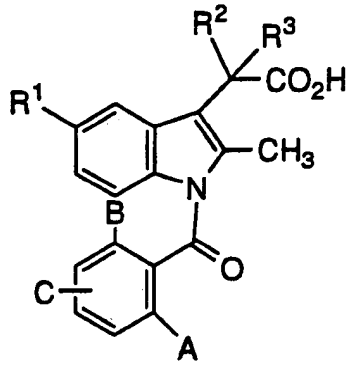


I

The invention also relates to certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula I; to a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I; and to process for the preparation of the novel compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The novel compound of this invention is represented by structural Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is -OCH_3, -$N(CH_3)_2$, -SCH_3, OCF_3, halo, or lower alkyl;

R^2 and R^3 are independently H or lower alkyl or R^2 and R^3 may be joined to form a saturated hydrocarbon ring of 3 to 7 members;

A is halogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, CF_3, CN, N_3, NO_2, SCF_3 or OCF_3;

B is A or also H if A is CF_3;

C is A or H with the proviso that if A is CF_3, B and C are not both H;

For purposes of the present specification the following terms have the indicated meanings.

"Lower alkyl" means alkyl groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclobutylmethyl, cycloheptyl, and the like.

"Lower alkoxy" means alkoxy groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration.

Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

"Lower alkylthio" means alkylthio groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, and the like. By way of illustration, the propylthio group signifies -$SCH_2CH_2CH_3$.

"Lower alkylsulfinyl" means those alkylsulfinyl groups of from 1 to 7 carbon atoms of straight, branched or cyclic configuration. Examples of lower alkylsulfinyl grups are methylsulfinyl, 2-butylsulfinyl, cyclohexylmethylsulfinyl, and the like. By way of illustration the 2-butylsulfinyl group signifies -$S(O)CH(CH_3)CH_2CH_3$.

"Lower alkylsulfonyl" means those alkylsulfonyl groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylsulfonyl groups are methylsulfonyl, 2-butylsulfonyl, cyclohexylmethylsulfonyl, and the like. By way of illustration the 2-butylsulfonyl group signifies -$S(O)_2CH(CH_3)CH_2CH_3$.

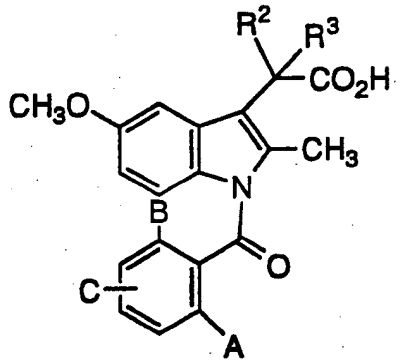
Halogen includes F, Cl, Br, and I.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers and mixtures thereof as well as their racemic and resolved, enantiomerically pure forms and other mixtures of the enantiomers and pharmaceutically acceptable salts thereof.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including

naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

One embodiment of the novel compounds of this invention is that with structural formula:

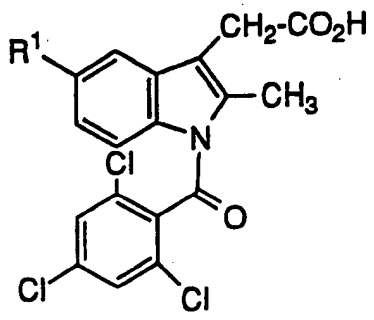


Specific compounds representative of this embodiment are those depicted in Table I.

Table I

A	B	C	R^2	R^3
Cl	Cl	4-Cl	H	H
Cl	Cl	4-Cl	CH_3	H
Cl	Cl	H	H	H
CF_3	H	4-CF_3	H	H
CF_3	CF_3	H	H	H
F	F	H	H	H
Cl	F	H	H	H
Br	Cl	H	CH_3	H
Br	Cl	4-Cl	H	H
CF_3	Cl	4-Cl	CH_3	CH_3
OCH_3	OCH_3	H	H	H
Cl	Cl	4-$S(O)_2CH_3$	H	H
Cl	Cl	4-SCH_3	H	H
Cl	Cl	4-$S(O)CH_3$	H	H
CH_3	CH_3	H	H	H
CH_3	Cl	4-Cl	H	H
NO_2	Cl	H	H	H
SCH_3	Cl	4-Cl	H	H
CN	Cl	H	H	H
I	Cl	H	H	H
N_3	Cl	H	H	H
SCF_3	Cl	4-Cl	H	H
OCF_3	Cl	H	H	H
$S(O)_2CH_3$	Cl	4-Br	H	H

Another embodiment of the novel compounds of the present invention is the compound of the following structure:



Specific compounds representative of this structure are indicated in Table II.

Table II

R^1
F
Cl
$CH(CH_3)_2$
$N(CH_3)_2$
S-CH_3
OCF_3

It will be understood that in the discussions of pharmaceutical compositions and methods of treatment which follow, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Another embodiment of this invention comprises the method of treatment using the Compound of Formula I for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries, and following surgical and dental procedures. In addition, the

novel compound may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. Compound 1 may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

Compound I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma.

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), compound I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

A fourth embodiment of this invention includes pharmaceutical compositions comprising the compound of Formula I as active ingredient. For the treatment of any of these cyclooxygenase mediated diseases compound I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

In further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically

effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetominophen or phenacetin; a potentiator including caffeine; an H2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effect amount of the compound of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the

gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethy-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax,

hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or

suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compound I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. For purposes of this application, topical application shall include mouth washes and gargles.

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of

administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In the process discussions and the Examples that follow, the following abbreviations have the indicated meanings:

DMAP	=	4-(dimethylamino)pyridine
HMPA	=	hexamethyl phosphoric triamide
KHMDS	=	potassium hexamethyldisilazane
NSAID	=	non-steroidal anti-inflammatory drug
r.t.	=	room temperature
rac.	=	racemic
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
C_3H_5	=	allyl
Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

The compounds of the present invention can be prepared according to the following methods.

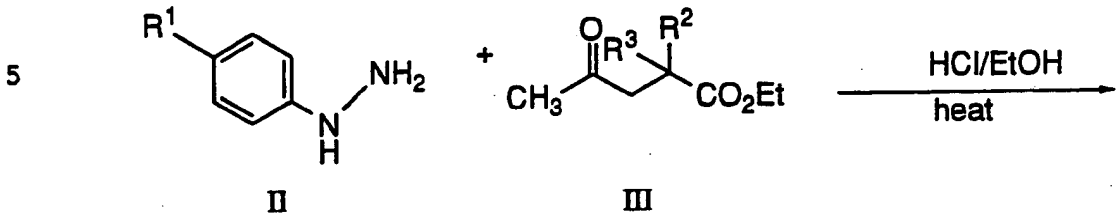
Method A

The indolyl compounds (IV) are easily prepared from the condensation of substituted phenylhydrazines II with substituted levulinic ethyl esters III, as described in a U.S. Patent # 3,161,654. After hydrolysis of the ester and esterification with 2-trimethylsilyl-ethanol in the presence of 1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide•HCl and DMAP, the ester derivatives V are obtained. The acylation of the nitrogen can be achieved by deprotonation of the nitrogen with KHMDS in THF/HMPA followed by the addition of an appropriate benzoyl chloride VI to afford VII. The 2-(trimethylsilyl)ethyl ester group can be then removed by fluoride treatment (TBAF).

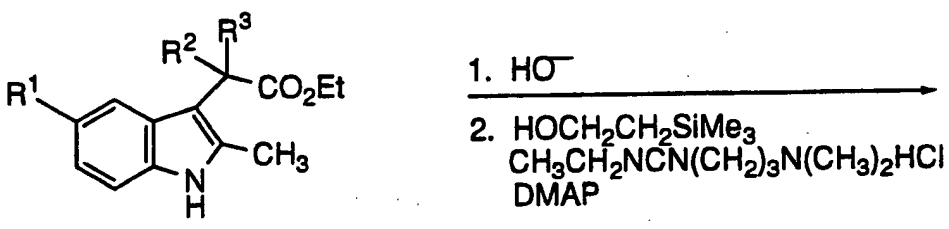
Method B

The formation of a saturated ring (X) may be accomplished from VII when R^2=R^3=H by deprotonation and bis-alkylation with a dihalogenated alkyl (Dox et al., J. Am. Chem. Soc. 1921, p. 2097 and Stewart et al., J. Org. Chem. 1965, p. 1451.

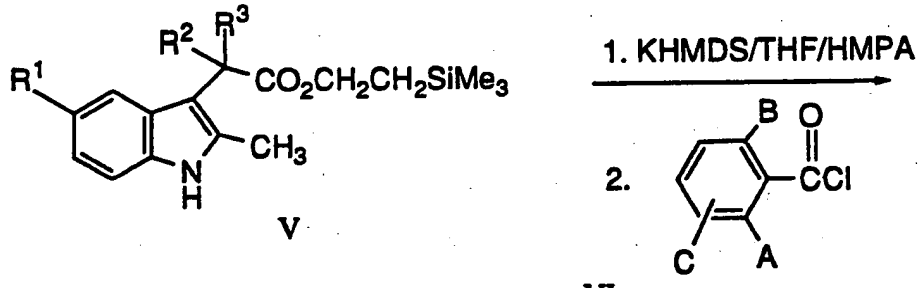
Method A



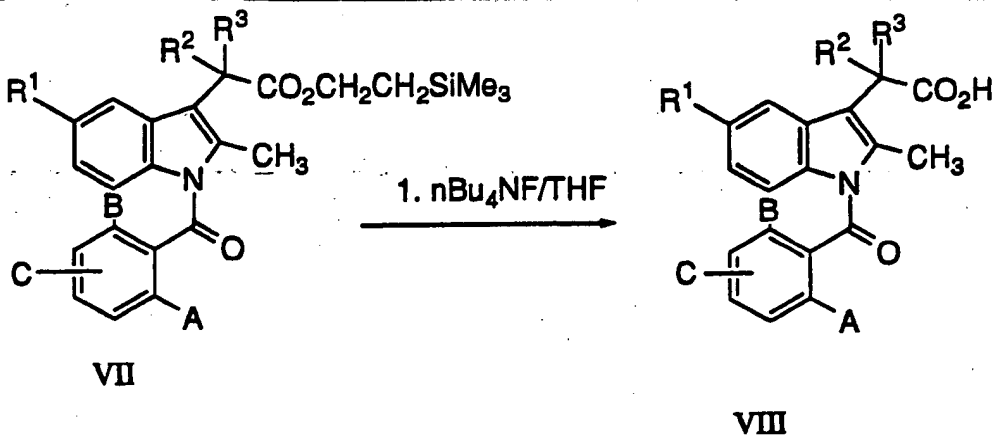
II III



IV

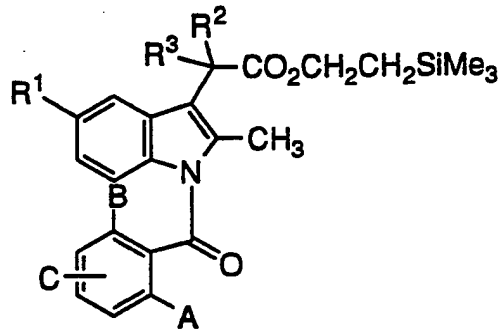


V VI



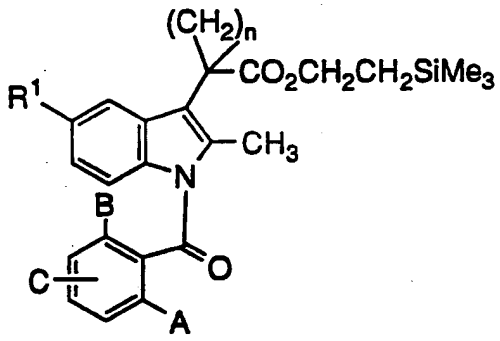
VII VIII

Method B



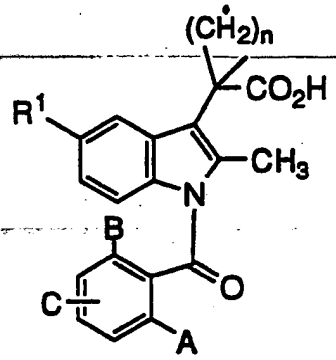
$X(CH_2)_nX$/ Base

VII R^2,R^3= H



1. nBuNF

IX



X

n= 2-6

The compound of Formula I can be tested using the following assays to determine their cyclooxygenase-2 inhibiting activity.

Inhibition of Cyclooxygenase Activity

Compounds were tested as inhibitors of cyclooxygenase activity in whole cell and microsomal cyclooxygenase assays. Both of these assays measured prostaglandin E_2 synthesis in response to arachidonic acid, using a radioimmunoassay. Cells used for whole cell assays, and from which microsomes were prepared for microsomal assays, were human osteosarcoma 143 cells (which specifically express cyclooxygenase-2) and human U-937 cells (which specifically express cyclooxygenase-1). In these assays, 100% activity is defined as the difference between prostaglandin E_2 synthesis in the absence and presence of arachidonate addition.

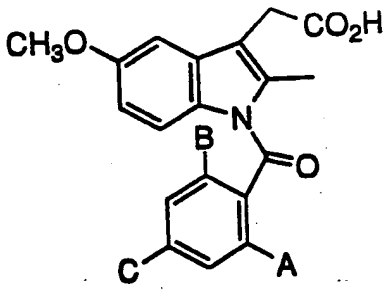
Rat Paw Edema Assay - Protocol

Male Sprague-Dawley rats (150-200 g) were fasted overnight and were given po either vehicle (1% methocel) or a test compound. One hr later, a line was drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V_o) was measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals were then injected subplantarly with 50 µl of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500 µg carrageenan per paw). Three hr later, the paw volume (V_3) was measured and the increases in paw volume ($V_3 - V_o$) were calculated. The animals were sacrificed by CO_2 aphyxiation and the absence or presence of stomach lesions scored. Data were compared with the vehicle-control values and percent inhibition calculated. Since a maximum of 60-70% inhibition (paw edema) was obtained with standard NSAIDs, ED_{30} values were

used for comparison. All treatment groups were coded to eliminate observer bias.

Compounds of the present invention are inhibitors of cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. The activities of the compounds against cyclooxygenase may be seen in the representative results shown below. In the assay, inhibition is determined by measuring the amount of prostaglandin E2 (PGE2) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a putative inhibitor. The IC50 values represent the concentration of putative inhibitor required to return PGE2 synthesis to 50% of that obtained as compared to the uninhibited control.

The results for inhibition of PGE2 production may be seen in Table III.



			IC_{50} (μM) Whole cell	
A	B	C	COX-1	COX-2
Cl	Cl	Cl	>100	1.0
Cl	Cl	H	>100	10.0

The invention is illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C,

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C.,

(iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;

(iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;

(vi) yields are given for illustration only;

(vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

EXAMPLE 1

1-(2,4,6-Trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid

Step 1: 5-Methoxy-2-methyl-3-indolyl acetic acid 2-(trimethylsilyl)ethyl ester

To a mixture of 5-methoxy-2-methyl-3-indolyl acetic acid (8.9 g, Aldrich) and 2-trimethylsilylethanol (7.0 mL) in dichloromethane (100 mL) at 0°C was added DMAP (500 mg) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.56 g) portionwise. After stirring overnight at room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with water (x2) and dried. The organic layer was evaporated to dryness and the residue was crystallized from EtOAc/hexane to give 9.3 g of the titled compound. Further reprocessing of the mother liquor afforded a further 2.0 g of the material to give a total of 11.3 g.

^1H NMR (acetone - d6) δ 0.02 (9H, s), 0.98 (2H, m), 2.38 (3H, s), 3.62 (2H, s), 3.78 (3H, s), 4.13 (2H, m), 6.66 (1H, dd), 6.97 (1H, d), 7.15 (1H, d), 9.70 (1H, bs).

Step 2: 1-(2,4,6-Trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid 2-(trimethylsilyl)ethyl ester

To 5-methoxy-2-methyl-3-indolyl acetic acid 2-(trimethylsilyl)ethyl ester (2.00 g) in THF (20.0 mL) was added HMPA (2.0 mL). To the resulting mixture at -78°C was added a 0.5M toluene solution of KHMDS (13.8 mL). After a period of 0.5 h, 2,4,6-trichlorobenzoyl chloride (1.03 mL) was added and the mixture was stirred 0.5 h at

-78°C then 0.5 h at 0°C. An aqueous solution of NH_4Cl was then added and extracted with EtOAc. After purification by flash chromatography (10% EtOAc in hexane) the title compound was obtained (2.80 g) and used as such for the next step.

Step 3: 1-(2,4,6-Trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid

To 1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid 2-(trimethylsilyl)ethyl ester (2.80 g) in THF (25.0 mL) at 0°C was added TBAF (14.7 mL). After a period of 5 h at room temperature, the reaction mixture was acidified by the addition of NH_4Cl and HCl, extracted with EtOAc, dried over Na_2SO_4 and evaporated. The resulting solid was washed with 10% EtOAc in hexane and recrystallized (EtOAc-hexane) to afford 1.73 g of the title compound, m.p. 193-196°C.

The following Examples were prepared according to the above-described methods.

EXAMPLE 2

1-(2,6-dichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid

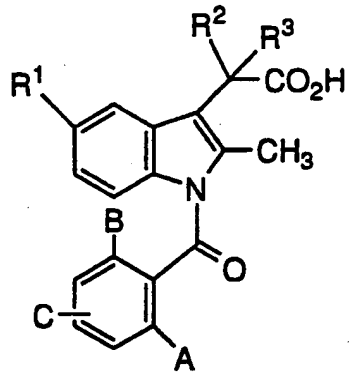
^1H NMR (400 MHz) CD_3COCD_3 mixture of rotamers in the ratio of 1.81.

Major rotamer δ 1.86 (3H, s), 3.70 (2H, s), 3.88 (3H, s), 6.97 (1H, m), 7.14 (1H, m), 7.65 (3H, m), 8.47 (1H, d).

Major rotamer δ 2.75 (3H, s), 3.77 (2H, s), 3.79 (3H, s), 5.96 (1H, d), 6.56 (1H, d), 7.15 (1H, m), 7.65 (3H, m).

WHAT IS CLAIMED IS:

1. A compound of structural formula:



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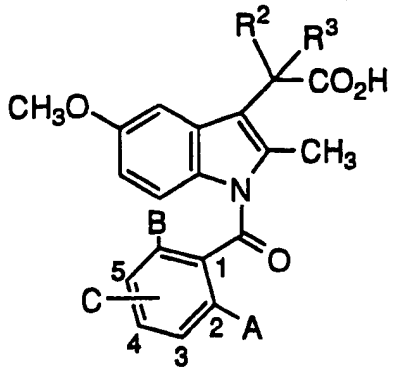
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-OCH_3$, $-N(CH_3)_2$, $-SCH_3$, $-OCF_3$, halo or lower alkyl;
R^2 and R^3 are independently H or lower alkyl or R^2 and R^3 may be joined to form a saturated hydrocarbon ring of 3 to 7 members;
A is halogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, CF_3, CN, N_3, NO_2, SCF_3 or OCF_3;
B is A or also H if A is CF_3;
C is A or H with the proviso that if A is CF_3, B and C are not both H;

2. The compound of Claim 1 of structural formula:

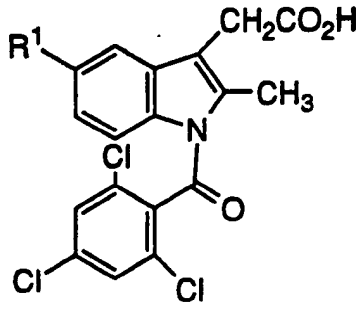


3. The compound of Claim 2 selected from the group consisting of those depicted in the following table:

Table I

A	B	C	R^2	R^3
Cl	Cl	4-Cl	H	H
Cl	Cl	4-Cl	CH_3	H
Cl	Cl	H	H	H
CF_3	H	4-CF_3	H	H
CF_3	CF_3	H	H	H
F	F	H	H	H
Cl	F	H	H	H
Br	Cl	H	CH_3	H
Br	Cl	4-Cl	H	H
CF_3	Cl	4-Cl	CH_3	CH_3
OCH_3	OCH_3	H	H	H
Cl	Cl	4-$S(O)_2CH_3$	H	H
Cl	Cl	4-SCH_3	H	H
Cl	Cl	4-$S(O)CH_3$	H	H
CH_3	CH_3	H	H	H
CH_3	Cl	4-Cl	H	H
NO_2	Cl	H	H	H
SCH_3	Cl	4-Cl	H	H
CN	Cl	H	H	H
I	Cl	H	H	H
N_3	Cl	H	H	H
SCF_3	Cl	4-Cl	H	H
OCF_3	Cl	H	H	H
$S(O)_2CH_3$	Cl	4-Br	H	H

4. The compound of claim 3 with structural formula:



5. The compound of Claim 4 selected from the group consisting of these wherein R^1 is -F, -Cl, $-CH(CH_3)_2$, $-N(CH_3)_2$, $-SCH_3$ or $-OCF_3$.

6. A pharmaceutical formulation comprising a pharmaceutically acceptable carrier and an effective cyclooxygenase-2 inhibitory amount of the compound of Claim 1.

7. A method of inhibiting cyclooxygenase-2 in a patient in need of such treatment which comprises the administration of an effective amount of the compound of Claim 1.

26

Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

Application number
GB 9422158.7

Relevant Technical Fields

(i) UK Cl (Ed.M) C2C (CUH)

(ii) Int Cl (Ed.5) C07D 209/26

Search Examiner
MR P DAVEY

Date of completion of Search
8 DECEMBER 1994

Databases (see below)
(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE DATABASES: CAS ONLINE

Documents considered relevant following a search in respect of Claims :-
1-7

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
X	Chemical Abstracts 106:50037 and JP 610148160 A2 (GREENCROSS CORP) see abstract	1,2,6,7

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).

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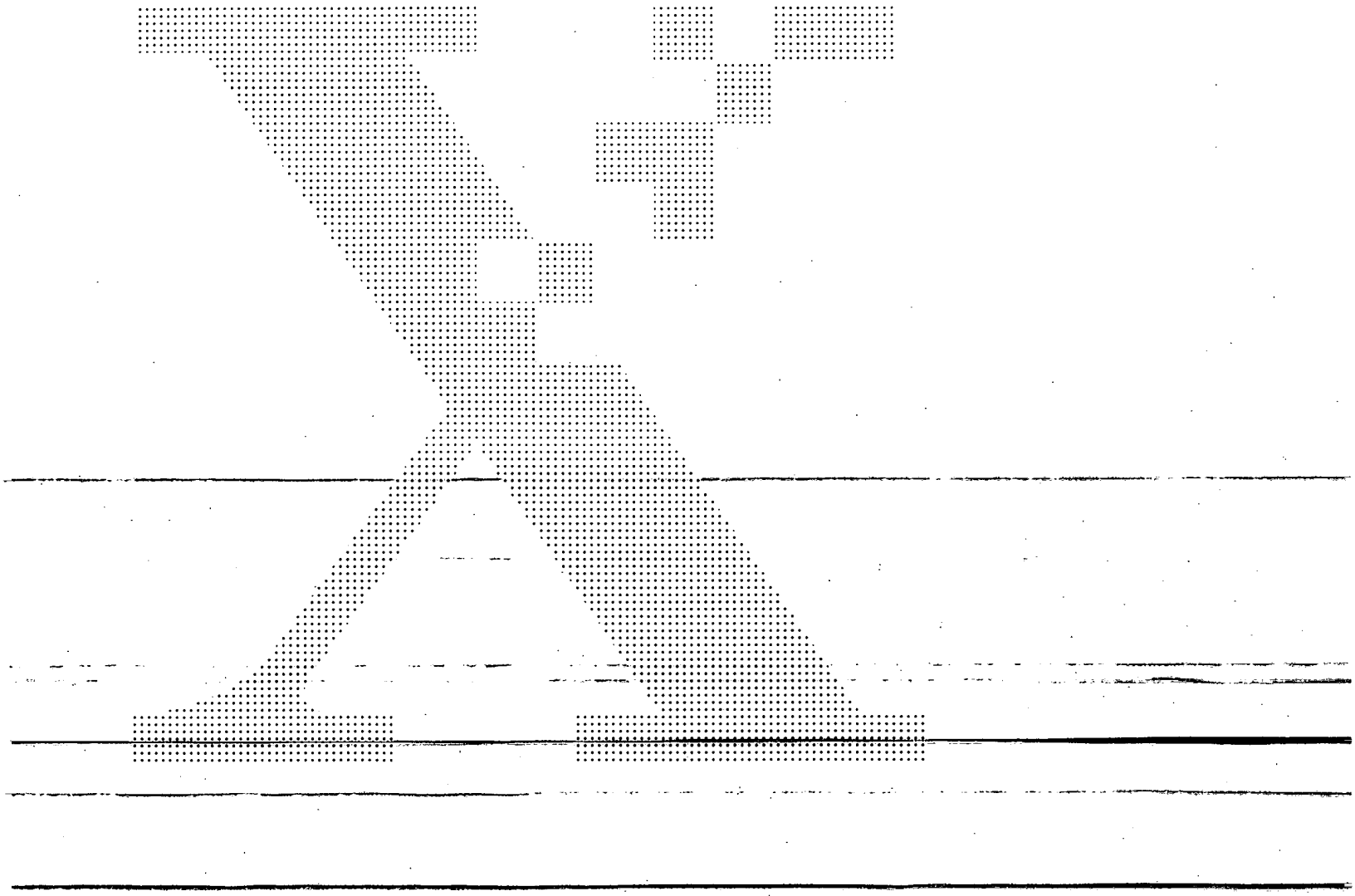

(12) UK Patent Application (19) GB (11) 2 294 879 (13) A

(43) Dat of A Publication 15.05.1996

(21) Application No 9520615.7

(22) Date of Filing 09.10.1995

(30) Priority Data
(31) 325759 (32) 19.10.1994 (33) US

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(51) INT CL[6]
A61K 31/34

(52) UK CL (Edition O)
A5B BHA B180 B33Y B332 B42Y B420 B48Y B480 B482 B484 B485 B50Y B503 B54Y B540 B55Y B551 B56Y B565 B57Y B576 B58Y B586 B60Y B606 B61Y B616 B65Y B650
U1S S2416

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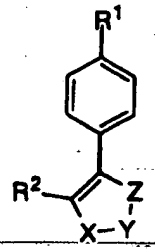
European J. Clin. Pharmacol. Vol. 47 (1) 1994. Suppl. A52

(58) Field of Search
UK CL (Edition O) A5B BHA BJA BJB
INT CL[6] A61K
ONLINE: CAS ONLINE, DIALOG/MEDICINE, WPI

(54) Cylcooxygenase-2 Inhibitors

(57) There are described cyclooxyenase-2 inhibitors for medical use, preferably for the treatment of bone disorders, particularly bone resorption. Preferably the inhibitors have the formula:



wherein R1 is selected from the group consisting of
(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)NHCH_3$,
(e) $S(O)NHNH_2$,
(f) $S(O)NHNHC(O)CF_3$,
and R2 is selected from the group consisting of
(a) C 1 - 6 alkyl,
(b) C3, C4, C5, C6, and C7, cycloalkyl,
(c) mono-, di or tri-substituted phenyl or naphthyl groups
or represent pharmaceutically acceptable salts thereof.

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TITLE OF THE INVENTION

METHOD OF PREVENTING BONE LOSS

BACKGROUND OF THE INVENTION

The invention relates to a method of inhibiting bone resorption, halting or retarding loss of bone mass, reducing fractures, improving bone repair and preventing or treating osteoporosis, particularly in post-menopausal women. Treatment of additional diseases/disorders is also disclosed.

The current major bone diseases of public concern include osteoporosis (post-menopausal, idiopathic and secondary to immobilization or drugs such as glucocorticoids), bone lesions due to metastases, hypercalcemia of malignancy, oral bone loss due to periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis and Paget's disease.

All these conditions are characterized by bone loss, resulting from an imbalance between bone resorption (breakdown) and bone formation. This process of bone remodeling or bone turnover continues throughout life and replaces about 14% of the skeletal mass per year on the average. However, the rate of bone turnover differs from site to site, for example, it is higher in the trabecular bone of the vertebrae and the alveolar bone in the jaws than in the cortices of the long bones. The potential for bone loss is directly related to turnover and can amount to over 5% per year in vertebrae immediately following menopause, a condition which leads to increased fracture risk.

There are currently 20 million people with detectable fractures of the vertebrae due to osteoporosis in the United States. In addition, there are 250,000 hip fractures per year attributed to osteoporosis. This clinical situation is associated with a 12-20% mortality rate within the first two years, while over 30% of the patients require nursing home care after the fracture.

Individuals suffering from all the conditions listed above would benefit from treatment with agents which inhibit bone resorption.

There is evidence in the literature that prostaglandins act as modulators of the bone resorption process. There is also evidence that certain non-steroidal anti-inflammatory agents (NSAID's) may (to some degree) reduce bone resorption. See, for example, the reports on the use of Diclofenac sodium by post menopausal women (*Am. J. Medicine*, Vol. 96, pp. 349-353, 1994); naproxen (*J. Bone Mineral Res.*, Vol. 5, pp. 1029-1035, 1990) in laboratory animal models.

As is appreciated by those of skill in the art, the natural processes of bone resorption and bone renewal are in constant dynamic equilibrium. This equilibrium, however, may differ with time (age), sex, and/or hormonal balance. Accordingly, the existence of evidence supporting the premise that the administration of an NSAID to post-menopausal women, may (to some degree) retard bone resorption, can not be taken as an indicator that the administration of NSAID's will affect a sufficient shift in equilibrium to halt or retard loss of bone mass, reduce fractures, improve bone repair or provide an effective means of preventing or treating osteoporosis. See in contrast GB 2,118,042 issued January 15, 1986 (US 4,621,077) , which discloses the use of bisphosphonates, including alendronate, which have been shown effective in the prevention of bone loss in post-menopausal women.

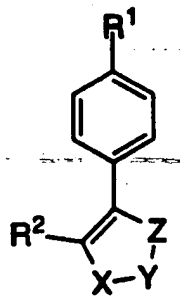
Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Up until recently, only one form of cyclooxygenase has been characterized, this corresponding to cyclooxygenase-1 or the constitutive enzyme, as originally identified in bovine seminal vesicles. Recently the gene for a second inducible form of cyclooxygenase (cyclooxygenase-2) has been cloned, sequenced and characterized from chicken, murine and human sources. This enzyme is distinct from the cyclooxygenase-1 which has now also been cloned, sequenced and characterized from sheep, murine and human sources. The second form of cyclooxygenase, cyclooxygenase-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones,

cytokines and growth factors. As prostaglandins have both physiological and pathological roles, evidence is mounting that the constitutive enzyme, cyclooxygenase-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, the inducible form, cyclooxygenase-2, appears to be mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines.

Surprisingly, the applicant has now found that selective cyclooxygenase-2 inhibitors, and in particular the compounds of formula I as described below are effective in inhibiting bone resorption, halting or retarding loss of bone mass, reducing fractures, improving bone repair and preventing or treating osteoporosis.

SUMMARY OF THE INVENTION

The invention encompasses a method of inhibiting bone resorption in patients in need of such inhibition to a degree sufficient to halt or retard loss of bone mass, reduce fractures, improve bone repair and prevent or treat osteoporosis comprising: the administration of a non-toxic therapeutically effective amount of a selective cyclooxygenase-2 inhibitor such as the compounds of formula I.

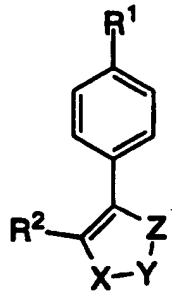


The invention also encompasses the treatment of additional diseases and disorders as disclosed herein.

The invention also encompasses pharmaceutical compositions for the purposes described herein.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses a method of inhibiting bone resorption in patients in need of such inhibition to a degree sufficient to either prevent, retard, halt or reverse loss of bone mass, thereby reducing the risk of fractures, comprising: the administration of a non-toxic therapeutically effective amount of a selective cyclooxygenase-2 inhibitor such as the compounds of Formula I



I

or a pharmaceutically acceptable salt thereof wherein:
X–Y–Z–is selected from the group consisting of:

(a) $-CR^5(R^{5'})-O-C(O)-$,
(b) $-C(O)-O-CR^5(R^{5'})-$,

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)(NH)CH_3$,
(e) $S(O)(NH)NH_2$,
(f) $S(O)(NH)NHC(O)CF_3$,
(g) $P(O)(CH_3)OH$, and
(h) $P(O)(CH_3)NH_2$,

R^2 is selected from the group consisting of

(a) C_{1-6}alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C_{1-6}alkoxy,

(4) C_{1-6}alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-6}alkyl,

(8) N_3,

(9) $-CO_2H$,

(10) $-CO_2-C_{1-4}$alkyl,

(11) $-C(R^3)(R^4)-OH$,

(12) $-C(R^3)(R^4)-O-C_{1-4}$alkyl, and

(13) $-C_{1-6}$alkyl$-CO_2-R^3$;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_{1-6}alkyl,

(4) C_{1-6}alkoxy,

(5) C_{1-6}alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

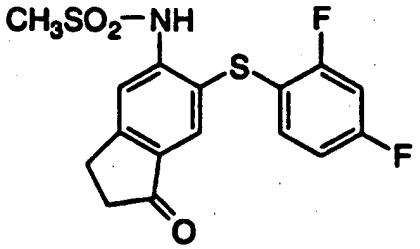
(9) -C(R^3)(R^4)-OH, and
(10) -C(R^3)(R^4)-O-C_{1-4}alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^3, R^4, R^5 and $R^{5'}$are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-6}alkyl.

For purposes of this specification a compound shall be defined as a selective cyclooxygenase-2 inhibitor if the ratio of it's IC_{50} for the inhibition of cyclooxygenase-1 divided by it's IC_{50} for the inhibition of cyclooxygenase-2, as measured as described in this specification or a comparable method is 200 or greater; preferably 1000 or greater. Accordingly, other selective cyclooxygenase-2 inhibitors within the scope of the invention include:



and other specific inhibitors discloses in WO 94/13635, published June 23, 1994; US 5,344,911, issued September 6, 1994; and WO 94/15932, published July 21 1994, all of which are hereby incorporated by reference.

In one genus the invention is directed to a method of preventing or treating osteoporosis, particularly in (but not limited to) post-monopausal women.

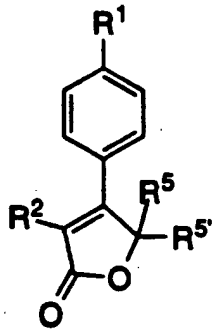
In a second genus the invention is directed to a method of inhibiting bone resorption in patients in need of such inhibition to a degree sufficient to substantially halt a loss of bone mass.

In a third genus the invention is directed to a method of reducing fractures in post-menopausal women or other patients who have suffered bone loss or have osteoporosis.

In a fourth genus the invention is directed to a method of maintaining bone density in post-menopausal women or other patients who susceptible to bone loss or have suffered bone loss or have osteoporosis.

Highly specific cyclooxygenase-2 inhibitors, such as compounds of formula I are also useful in the treatment of hypercalcemia of malignancy, osteolysis due to bone metastases, oral bone loss due to periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, and secondary forms of osteoporosis such as immobilization-induced osteoporosis and osteoporosis resulting from glucocorticoid treatment, hyperthyroidism and thyroid hormone (T_3, T_4) treatment.

Each of these categories embraces the use of compounds of Formula Ia



Ia

or pharmaceutically acceptable salts thereof wherein:

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)NHCH_3$,
(e) $S(O)NHNH_2$, and
(f) $S(O)NHNHC(O)CF_3$;

R^2 is selected from the group consisting of

(a) C_{1-6}alkyl,
(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
(c) mono- or di-substituted phenyl wherein the substituent is selected from the group consisting of
(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,
(9) $-CO_2H$,
(10) $-CO_2-C_{1-4}$alkyl,
(11) $-C(R^3)(R^4)-OH$,
(12) $-C(R^3)(R^4)-O-C_{1-4}$alkyl, and
(13) $-C_{1-6}$alkyl$-CO_2-R^3$;
(d) heteroaryl
(e) benzoheteroaryl

R^3, R^4, R^5 and $R^{5'}$ are each independently selected from the group consisting of
(a) hydrogen,
(b) C_{1-6}alkyl.

Within this class is the sub-class of compounds of Formula Ia wherein

R^1 is selected from the group consisting of
(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)NHCH_3$,
(e) $S(O)NHNH_2$, and
(f) $S(O)NHNHC(O)CF_3$;

R^2 is selected from the group consisting of

(a) C_{1-4}alkyl,
(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
(c) mono- or di-substituted phenyl wherein the substituent is selected from the group consisting of
    (1) hydrogen,
    (2) fluoro, chloro, and bromo,
    (3) C_{1-4}alkoxy,
    (4) C_{1-4}alkylthio,
    (5) CN,
    (6) CF_3,
    (7) C_{1-4}alkyl,
    (8) N_3,
    (9) $-CO_2H$,
    (10) $-CO_2-C_{1-3}$alkyl,
    (11) $-C(R^3)(R^4)-OH$, and
    (12) $-C(R^3)(R^4)-O-C_{1-3}$alkyl,
(d) mono- or di-substituted heteroaryl selected from the group consisting of
    (1) furanyl,
    (2) diazinyl, triazinyl and tetrazinyl,
    (3) imidazolyl,
    (4) isooxazolyl,
    (5) isothiazolyl,
    (6) oxadiazolyl,
    (7) oxazolyl,
    (8) pyrazolyl,
    (9) pyrrolyl,
    (10) thiadiazolyl,
    (11) thiazolyl,
    (12) thienyl,
    (13) triazolyl, and
    (14) tetrazolyl,

wherein said substituents are selected from the group consisting of

(a) hydrogen,
(b) fluoro, chloro, bromo,
(c) C_{1-4}alkoxy,
(d) C_{1-4}alkylthio,
(e) CN,
(5) CF_3,
(6) C_{1-4}alkyl,
(7) N_3,
(8) $-C(R^3)(R^4)-OH$,
(9) $-C(R^3)(R^4)-O-C_{1-4}$alkyl.

Within this sub-class is the group of compounds of Formula Ia wherein

R^2 is selected from the group consisting of

(a) cyclohexyl, and
(b) mono- or di-substituted phenyl, and wherein the substituents are selected from the group consisting of
(1) hydrogen,
(2) halo,
(3) C_{1-4}alkoxy,
(4) C_{1-4}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-4}alkyl,
(8) N_3, and
(9) $-C(R^3)(R^4)-OH$;

R^3 and R^4, are each independently selected from the group consisting of

(a) hydrogen,
(b) methyl or ethyl,

R^5 and $R^{5'}$ are each hydrogen.

Within this sub-class are the compounds of Formula Ia wherein:

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,

(b) $S(O)_2NH_2$,

(c) $S(O)NHCH_3$, and

(d) $S(O)NHNH_2$;

R^2 is selected from the group consisting of

mono or di-substituted phenyl wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo, selected from the group consisting of fluoro, chloro and bromo,

(3) C_{1-3}alkoxy,

(4) C_{1-3}alkylthio,

(5) CN, and

(6) C_{1-3}alkyl;

Within this group are the compounds of Formula Ia wherein

R^2 is

mono or di-substituted phenyl wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo, selected from the group consisting of fluoro, chloro and bromo,

(3) methoxy, and

(4) methyl.

These compounds may be more particularly defined as the compounds of Formula Ia wherein

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$, and

(b) $S(O)_2NH_2$,

R^2 is

mono or di-substituted phenyl wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo.

For purposes of this specification mono- or di-substituted heteroaryl of definition R^2 is defined as a mono- or di-substituted heteroaryl selected from the group consisting of
(1) 2-furanyl,
(2) 3-furanyl,
(3) 2-thienyl,
(4) 3-thienyl,
(5) 3-isoxazolyl,
(6) 4-isoxazolyl,
(7) 5-isoxazolyl,
(8) 3-isothiazolyl,
(9) 4-isothiazolyl,
(10) 5-isothiazolyl,
(11) 2-oxazolyl,
(12) 4-oxazolyl,
(13) 5-oxazolyl,
(14) 2-thiazolyl,
(15) 4-thiazolyl,
(16) 5-thiazolyl,
(17) 1,2,3-thiadiazol-4-yl,
(18) 1,2,3-thiadiazol-5-yl,
(19) 1,2,4-thiadiazol-3-yl,
(20) 1,2,4-thiadiazol-5-yl,
(21) 1,3,4-thiadiazol-2-yl,
(22) 1,2,5-thiadiazol-3-yl,
(23) 1,2,3-oxadiazol-4-yl,
(24) 1,2,3-oxadiazol-5-yl,
(25) 1,2,4-oxadiazol-3-yl,
(26) 1,2,4-oxadiazol-5-yl,
(27) 1,3,4-oxadiazol-2-yl,

(28) 1,2,5-oxadiazol-3-yl,
(29) pyrazol-4-yl,
(30) pyrazol-4-yl,
(31) pyrazol-5-yl,
(32) 1,2,3-triadiazol-4-yl,
(33) 1,2,3-triadiazol-5-yl,
(34) 1,2,4-triadiazol-3-yl,
(35) 1,2,4-triadiazol-5-yl,
(36) 1,2-diazinyl,
(37) 1,3-diazinyl,
(38) 1,4-diazinyl,
(39) 1,2,3,4-tetrazin-5-yl,
(40) 1,2,4,5-tetrazin-4-yl,
(41) 1,3,4,5-tetrazin-2-yl,and
(42) 1,2,3,5-tetrazin-4-yl,

wherein the substituents are defined in any defintion of R^2.

Within the mono- or di-substituted heteroaryl of R^2 is the group wherein the substituents are selected from the group consisting of

(a) hydrogen,
(b) fluoro or chloro,
(c) C_{1-3}alkoxy,
(d) C_{1-6}alkylthio,
(e) CN,
(5) CF_3,
(6) C_{1-3}alkyl,
(7) $-C(R^3)(R^4)-OH$;
(8) $-C(R^3)(R^4)-O-C_{1-4}$alkyl.

Within the mono- or di-substituted heteroaryl of R_2 immediately above, is the group wherein the heterocycles are selected from

(1) 3-isoxazolyl,
(2) 4-isoxazolyl,

(3) 5-isoxazolyl,
(4) 3-isothiazolyl,
(5) 4-isothiazolyl,
(6) 5-isothiazolyl,
(7) 2-oxazolyl,
(8) 4-oxazolyl,
(9) 5-oxazolyl,
(10) 2-thiazolyl,
(11) 4-thiazolyl,
(12) 5-thiazolyl,
(13) 1,2,3-thiadiazol-4-yl,
(14) 1,2,3-thiadiazol-5-yl,
(15) 1,2,4-thiadiazol-3-yl,
(16) 1,2,4-thiadiazol-5-yl,
(17) 1,3,4-thiadiazol-2-yl,
(18) 1,2,5-thiadiazol-3-yl,
(19) 1,2,3-oxadiazol-4-yl,
(20) 1,2,3-oxadiazol-5-yl,
(21) 1,2,4-oxadiazol-3-yl,
(22) 1,2,4-oxadiazol-5-yl,
(23) 1,3,4-oxadiazol-2-yl,
(24) 1,2,5-oxadiazol-3-yl,
(25) 1,2-diazinyl,
(26) 1,3-diazinyl, and
(27) 1,4-diazinyl.

Within the mono- or di-substituted heteroaryl of R^2 immediately above, is the group wherein the heterocycles are selected from

(1) 3-isothiazolyl,
(2) 4-isothiazolyl,
(3) 5-isothiazolyl,
(4) 2-oxazolyl,
(5) 4-oxazolyl,

(6) 5-oxazolyl,
(7) 2-thiazolyl,
(8) 4-thiazolyl,
(9) 5-thiazolyl,
(10) 1,2-diazinyl,
(11) 1,3-diazinyl, and
(12) 1,4-diazinyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,
(2) fluoro or chloro,
(3) C_{1-3}alkoxy,
(4) C_{1-3}alkylthio,
(5) CN,
(6) C_{1-3}alkyl, and
(7) $-C(R^3)(R^4)-OH$,

wherein R^3 and R^4 are each independently hydrogen, methyl or ethyl.

For purposes of this specification alkyl is defined to include linear, branched, and cyclic structures, with C_{1-6}alkyl including including methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, C_{1-6}alkoxy is intended to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Likewise, C_{1-6}alkylthio is intended to include alkylthio groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$.

Exemplifying the invention are:

(a) 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone,

(b) 3-(4-Fluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(*5H*)-furanone,

(c) 5,5-Dimethyl-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(d) 3-(3-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(e) 5,5-Dimethyl-3-(3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(f) 5,5-Dimethyl-3-(3-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(g) 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(h) 3-(3,4-Dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(i) 5,5-Dimethyl-3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(j) 5,5-Dimethyl-3-(3,4-dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(k) 5,5-Dimethyl-3-(4-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(l) 3-(2-Naphyhyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(m) 5,5-Dimethyl-3-(2-naphyhyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(m) 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone.

Further illustrating the invention are 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone, and 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone, or a pharmaceutically acceptable salt thereof.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

In a second embodiment, the invention encompasses pharmaceutical compositions for treatment of osteoporosis.

Within this embodiment the invention encompasses pharmaceutical compositions for treatment of osteoporosis comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine,

piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

As indicated above, pharmaceutical compositions for treating osteoporosis as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxy-propylmethy-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active

ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-

irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 100 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 6 g per patient per day. For example, osteoporosis may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day, preferably 2.5 mg to 1 g per patient per day. A dosage 1.0 to 100 mg/kg per day or 1.0 to 20 mg/kg per day may prove especially useful.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

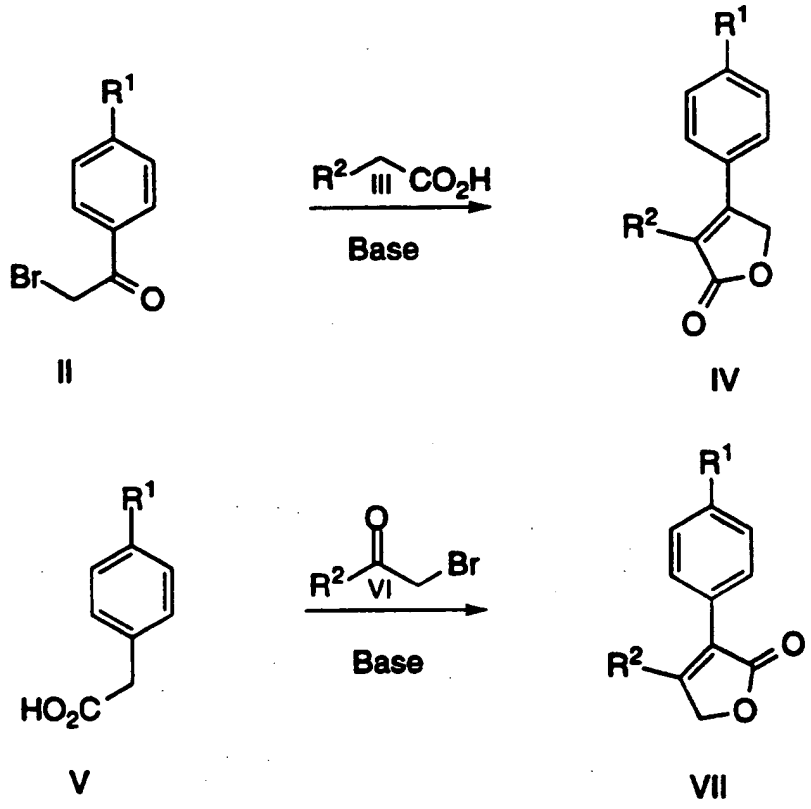
Methods of Synthesis

The compounds of the present invention can be prepared according to the following methods.

Method A:

An appropriately substituted aryl bromomethyl ketone II is reacted with an appropriately substituted aryl acetic acid III in a solvent such as acetonitrile in the presence of a base such as triethylamine and then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the lactone IV. Isomeric lactone VII is prepared by reacting phenylacetic acid V with bromoketone VI under similar conditions.

METHOD A

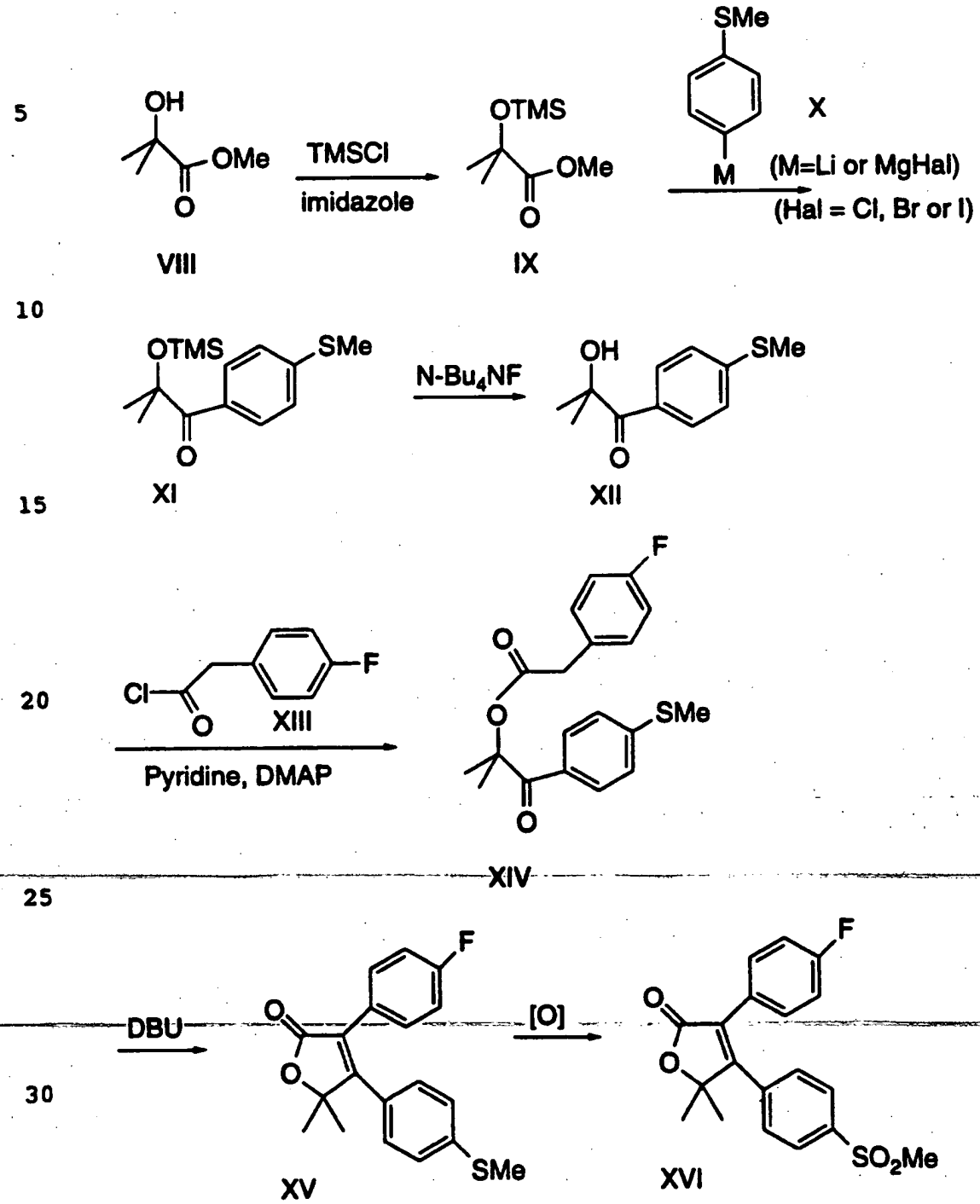


(R^2 is a mono- or disubstituted phenyl or a mono- or disubstituted heteroaryl)

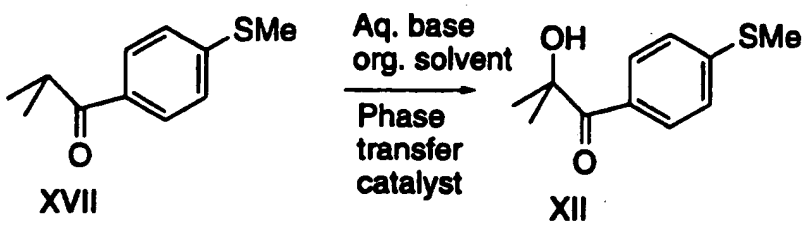
Method B:

Methyl-2-hydroxy-isobutyrate VIII is silylated with TMSCl to give the TMS ether IX, which is treated with the organomatallic X to provide ketone XI. Desilylation followed by acylation yields keto-ester XIV, which can be cyclized to lactone XV by base catalysis. Oxidation of XV with MMPP or mCPBA affords the desired product XVI.

METHOD B

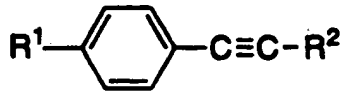

OH
OMe
O
VIII
TMSCl
imidazole
OTMS
OMe
O
IX
SMe
X
M
(M=Li or MgHal)
(Hal = Cl, Br or I)
OTMS
SMe
O
XI
N-Bu4NF
OH
SMe
O
XII
Cl
O
F
XIII
Pyridine, DMAP
F
O
O
SMe
O
XIV
DBU
F
O
O
SMe
XV
[O]
F
O
O
SO2Me
XVI

METHOD C

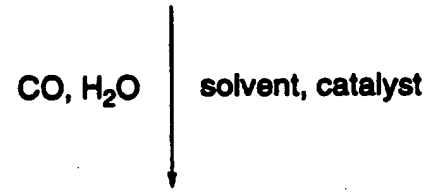


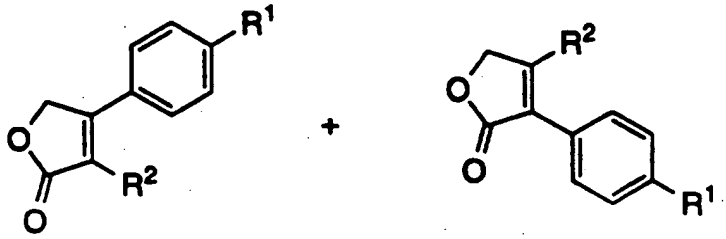
An alternative preparation of the hydroxy ketone XII is the oxidation of the known (*J. Org. Chem.* **1991** *56*, 5955-8; *Sulfur Lett.* **1991**, *12*, 123-32) ketone XVII. A mixture of XVII, aqueous base, such as NaOH, organic solvents such as carbon tetrachloride/-toluene and a phase transfer catalyst such as ALIQUAT 336 is stirred in air at room temperature to provide XII. Compound XII is also described in U.S. 4,321,118 and *Org. Coat. 1986, 6*, 175-95.

METHOD D



XVIII

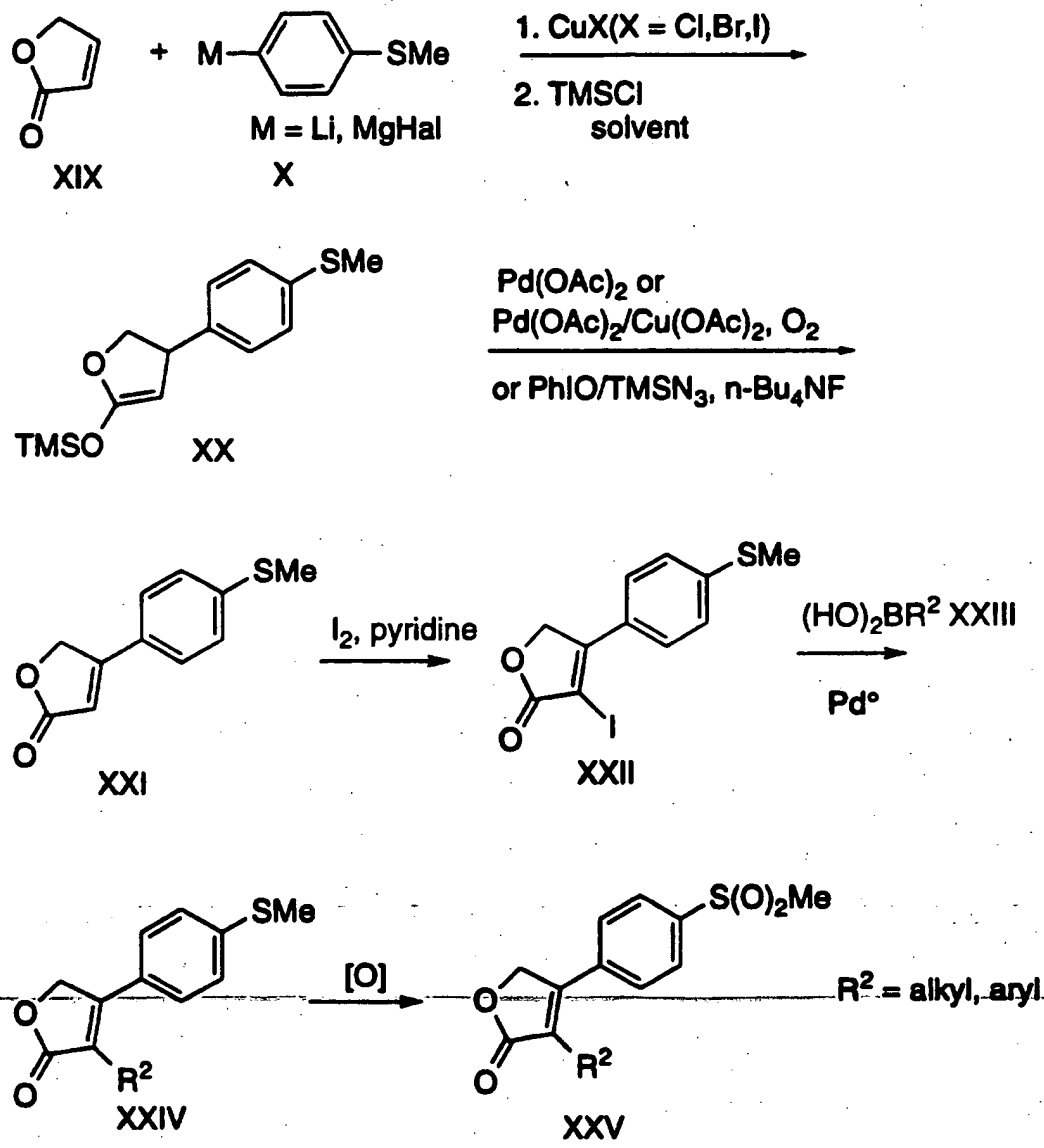




IV VII

By reacting an acetylene XVIII with carbon monoxide and water in the presence of suitable catalysts, a mixture of compound IV and its isomer VII is obtained. The isomers are separable by standard procedures in the art such as chromatography or crystallization. Examples of useful catalysts and conditions are $PdCl_2$ in aqueous HCl and EtOH, heated at 50-150°C and 50-150 atmospheres of pressure, or $Rh_4(CO)_{12}$ (or $Rh_6(CO)_{16}$) in aqueous THF (or acetone, acetonitrile, benzene, toluene, EtOH, MeOH) containing a trialkylamine, at 50-150°C and 20-300 atmospheres pressure. See Takahashi *et al.*, *Organometallics* **1991**, *10*, 2493-2498; and Tsuji *et al.*, *J. Am. Chem. Soc.* **1966**, *88*, 1289-1292.

METHOD E



1, 4-Addition to XIX of 4-methylthiophenyl organometallic reagents X in the presence of copper salts and the trapping of the resultant enolate with trialkyl silyl chloride such as TMSCl or TIPSCl provide the ketene acetal XX. The ketene acetal can then be oxidized to the substituted butenolide XXI by the method of Ito using $Pd(OAc)_2$ or catalytic amounts of $Pd(OAc)_2$ and $Cu(OAc)_2$ with O_2 in MeOH or by the method of Magnus using $PhIO/TMSN_3$ and Bu_4NF. Introduction of

the iodine can be accomplished by treating XXI with I_2 in the presence of pyridine to afford XXII. Palladium catalyzed Suzuki or Stille coupling of XXIII with the appropriate aryl or alkyl partner such as the boronic acid XXIII provides the butenolide XXIV. The sulfide can be oxidized to a sulfone by various oxidizing agents such as peracetic acid, MPPM, MMPP or H_2O_2 to give the desired compound XXV. See Y. Ito *et al.*, *J. Am. Chem. Soc.* **1979**,*101*, 494, footnote 2; and P. Magnus *et al.*, *Tet. Lett.* **1992**, 2933.

Representative Compounds

Tables I and II illustrate compounds of Formula I.

TABLE I

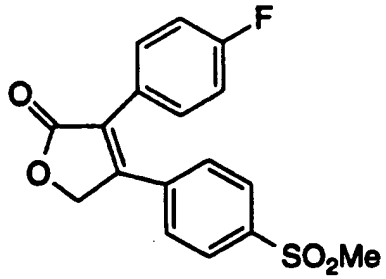
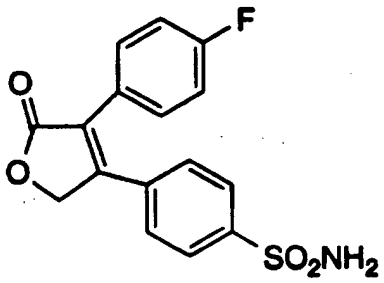
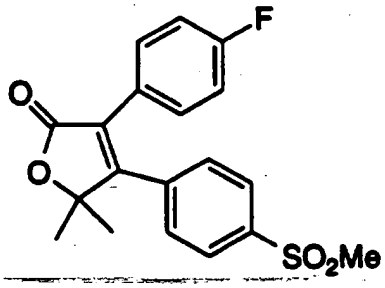
		Example	Method
5		1	A
10			
15		2	A
20		3	B
25			
30			

TABLE I (continued)

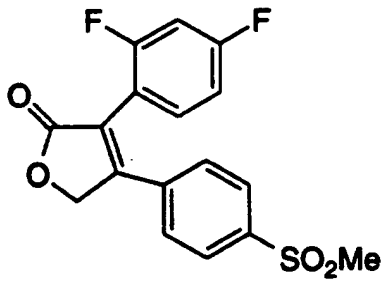
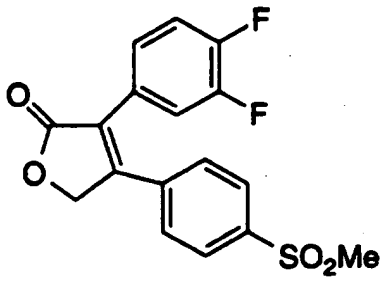
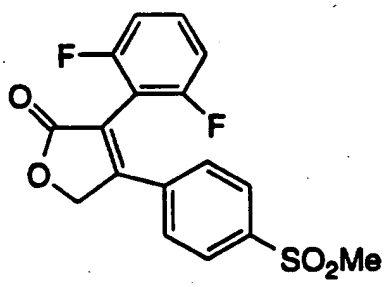
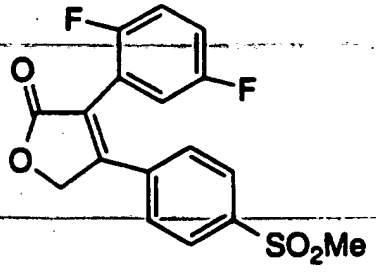
	Example	Method
	4	A
	5	A
	6	A
	7	A

TABLE I (continued)

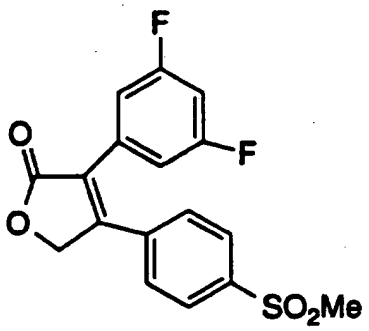
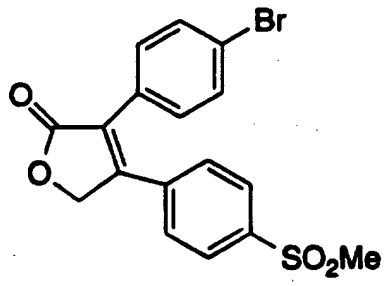
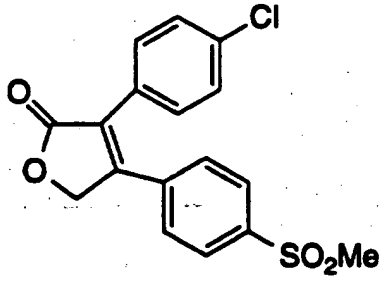
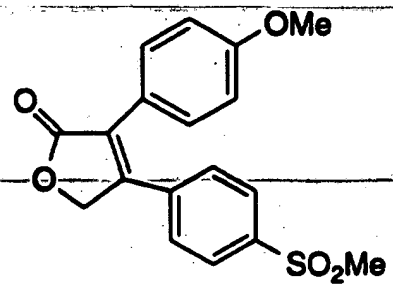
		Example	Method
		8	A
		9	A
		10	A
		11	A

TABLE I (continued)

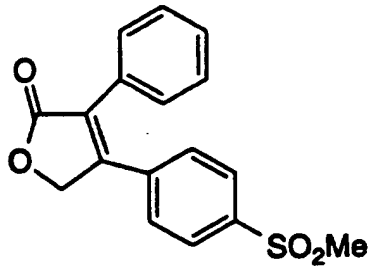
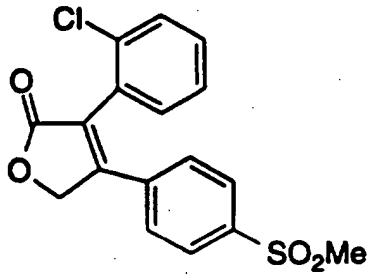
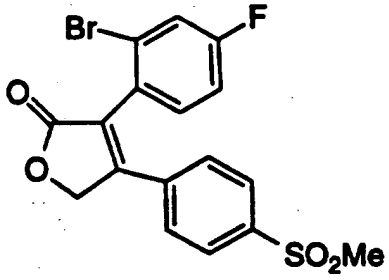
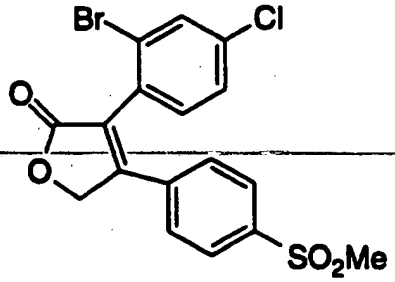
	Example	Method
	12	A
	13	A
	14	A
	15	A

TABLE I (continued)

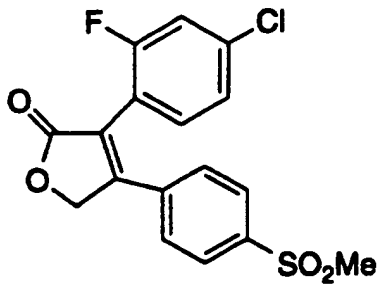
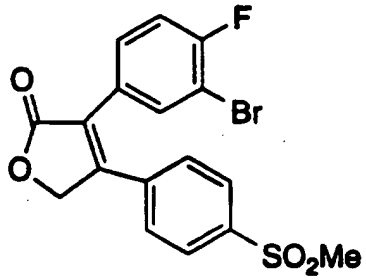
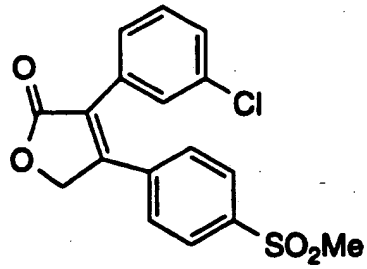
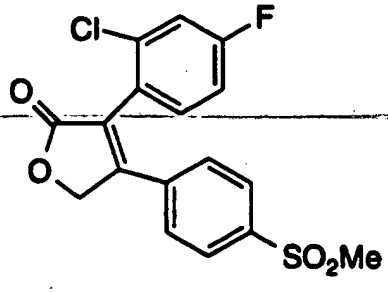
	Example	Method
	16	A
	17	A
	18	A
	19	A

TABLE I (continued)

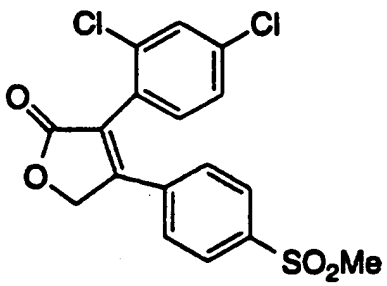
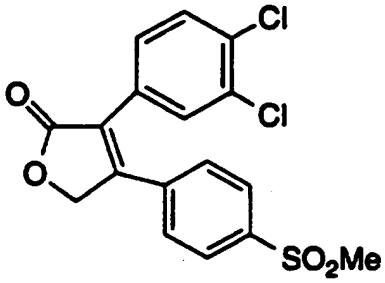
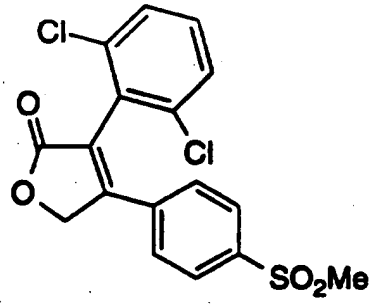
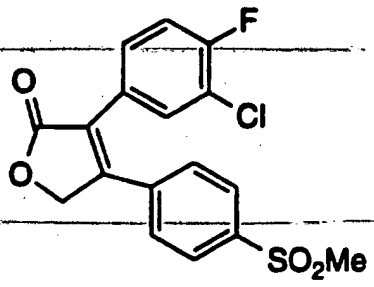
		Example	Method
		20	A
		21	A
		22	A
		23	A

TABLE I (continued)

Table I (continued)

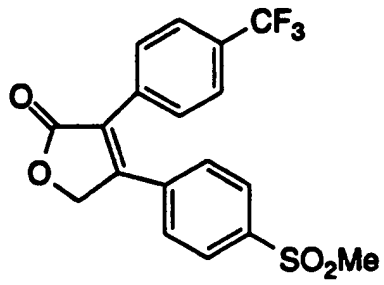
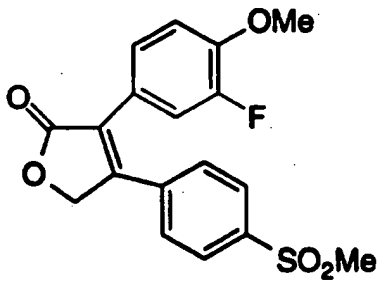
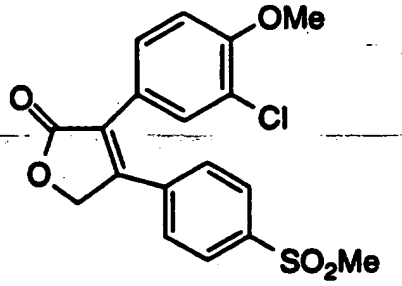
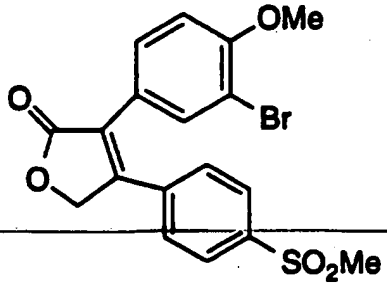
		Example	Method
		24	A
		25	A
		26	A
		27	A

TABLE I (continued)

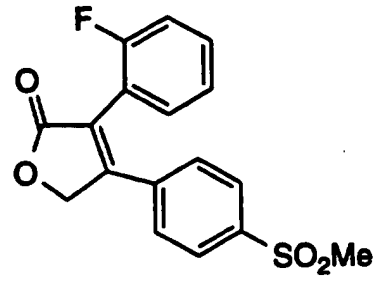
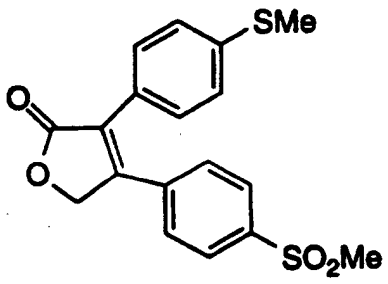
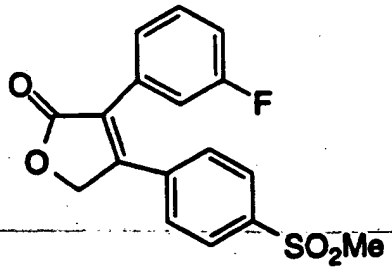
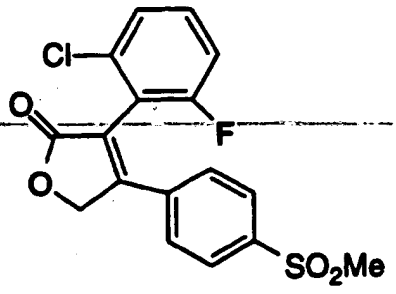
	Example	Method
	28	A
	29	A
	30	A
	31	A

TABLE I (continued)

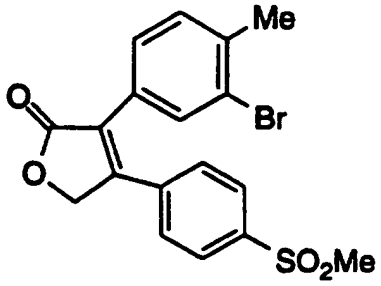
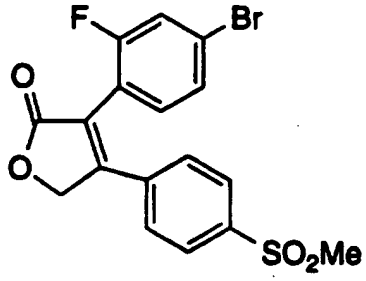
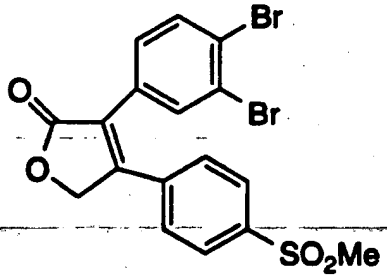
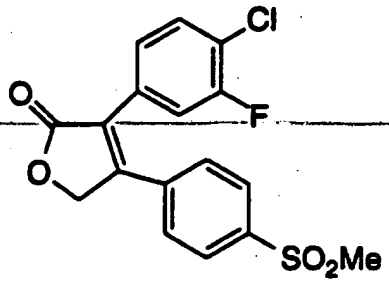
		Example	Method
		32	A
		33	A
		34	A
		35	A

TABLE I (continued)

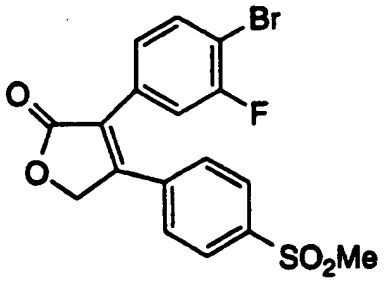
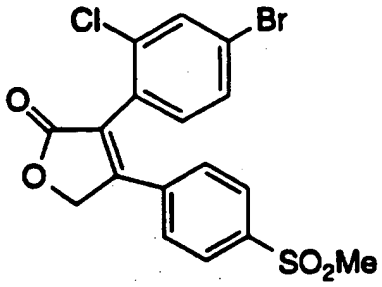
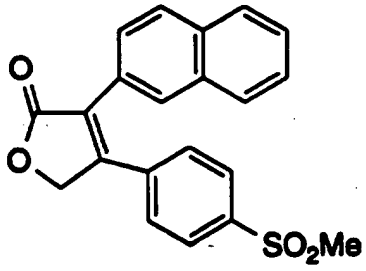
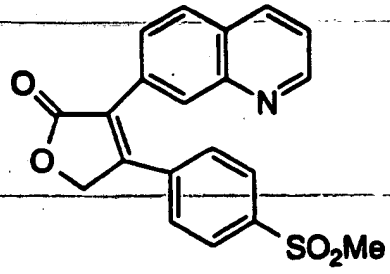
		36	A
		37	A
		38	A
		39	A

TABLE I (continued)

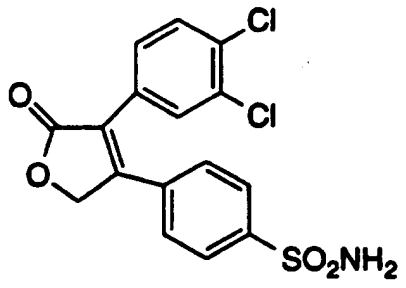
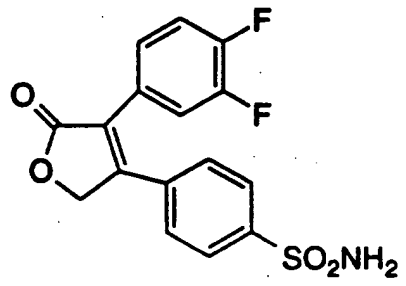
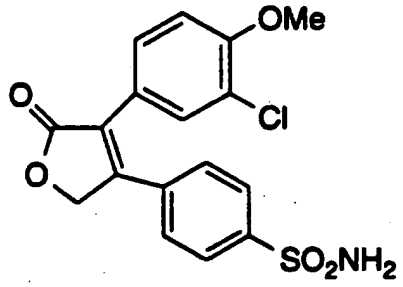
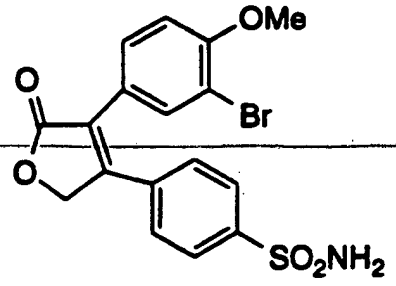
		Example	Method
		40	A
		41	A
		42	A
		43	A

TABLE I (continued)

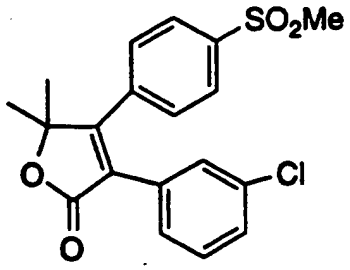
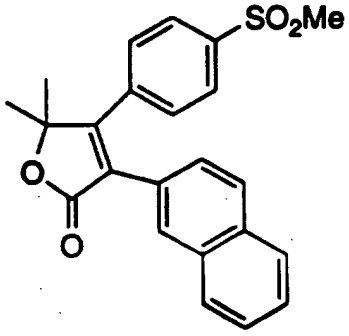
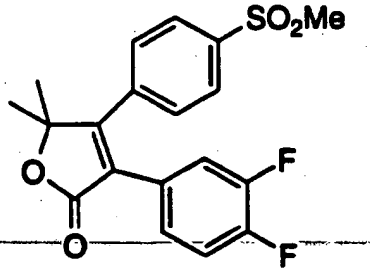
	Example	Method
	44	B + C
	45	B + C
	46	B + C

TABLE I (continued)

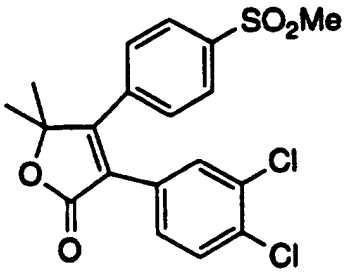
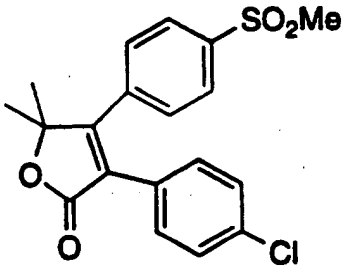
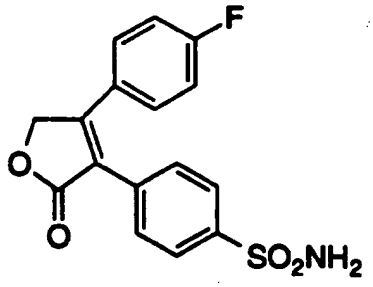
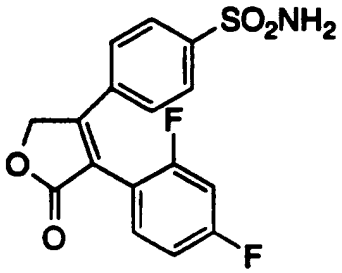
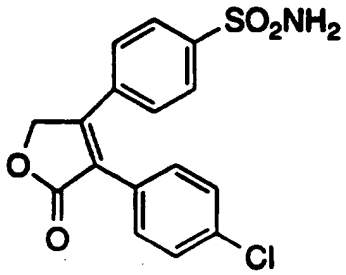
	Example	Method
	47	B + C
	48	B+ C

TABLE II







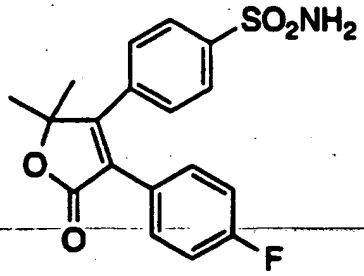


TABLE II (continued)

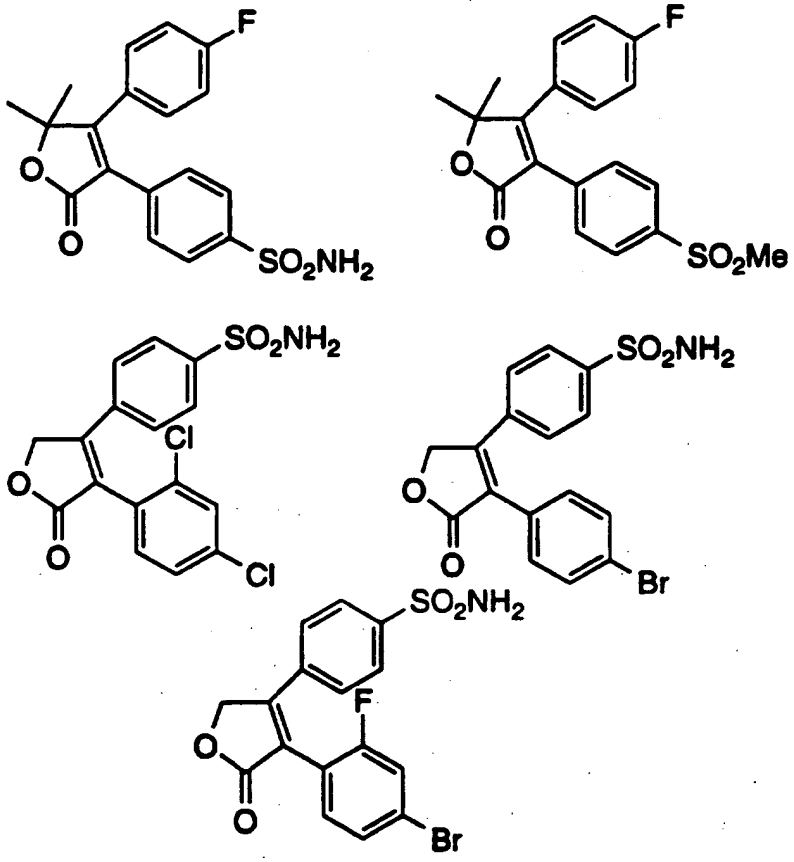
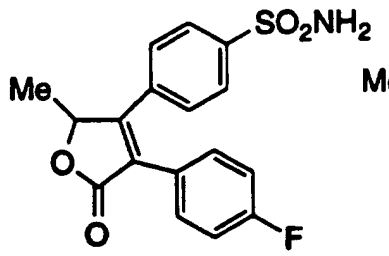
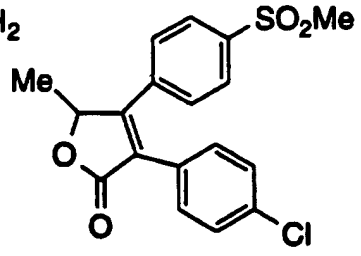
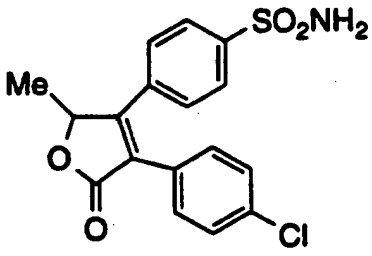
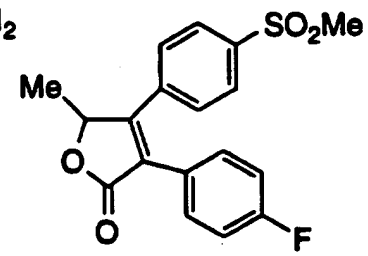


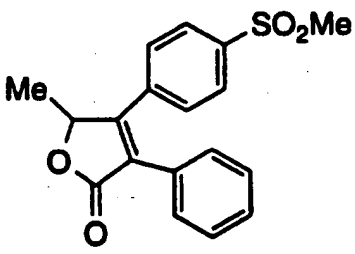
TABLE II (continued)











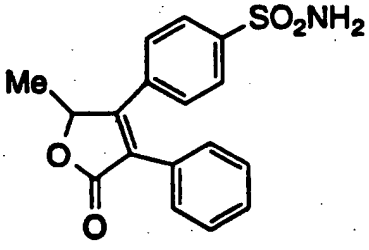
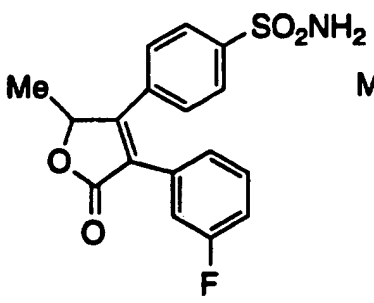
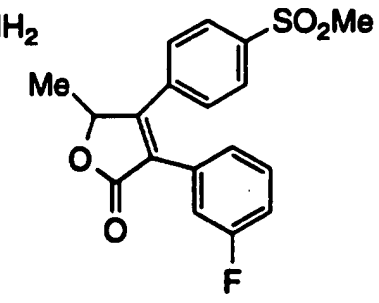
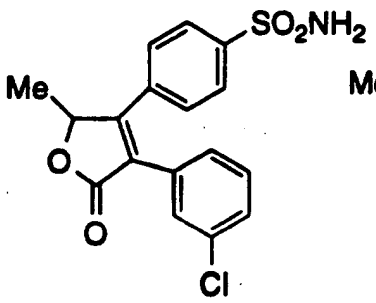
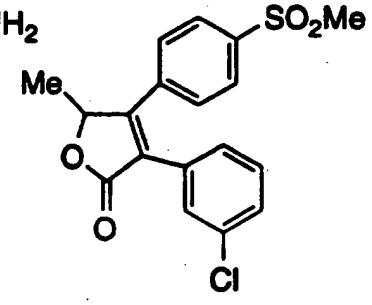


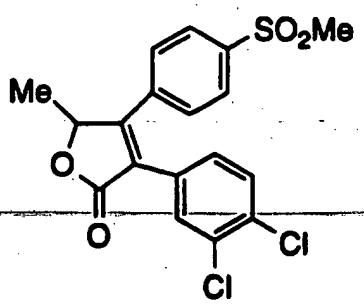
TABLE II (continued)











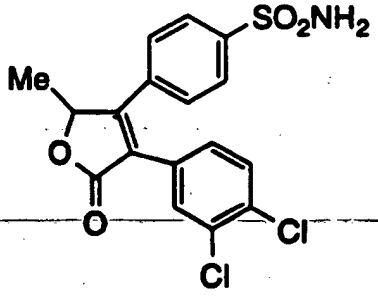
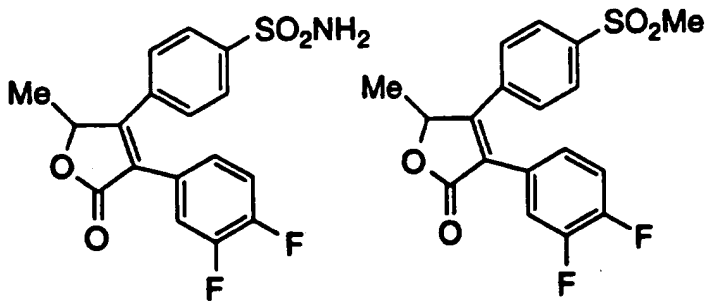
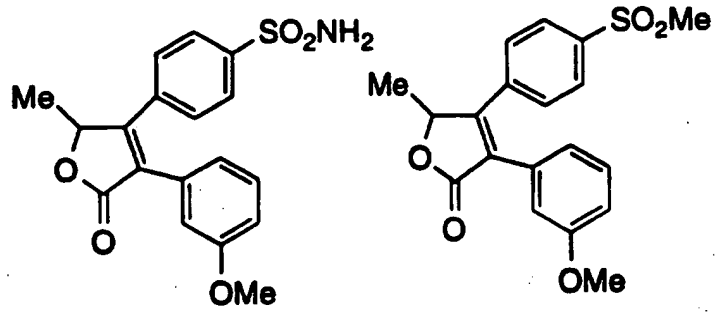
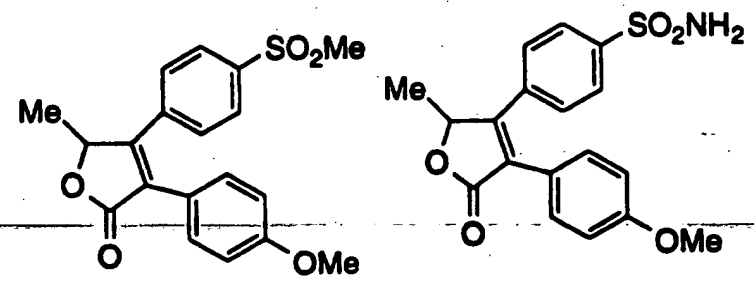


TABLE II (concluded)







The compounds of the invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60 C; the course of reactions was followed by thin layer

chromatography (TLC) and reaction times are given for illustration only; melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations; the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; yields are given for illustration only; when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal; chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

The following abbreviations have the indicated meanings:

Ac	=	acetyl
Bn	=	benzyl
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	=	diisobutylaluminum hydride
DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
Et_3N	=	triethylamine
LDA	=	lithium diisopropylamide
m-CPBA	=	metachloroperbenzoic acid
MMPP	=	monoperoxyphtalic acid
MPPM	=	monoperoxyphthalic acid, magnesium salt $6H_2O$
Ms	=	methanesulfonyl = mesyl = SO_2Me
Ms0	=	methanesulfonate = mesylate

NSAID	=	non-steroidal anti-inflammatory drug
OXONE®	=	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
Ph	=	phenyl
Phe	=	benzenediyl
Pye	=	pyridinediyl
r.t	=	room temperature
rac.	=	racemic
SAM	=	aminosulfonyl or sulfonamide or SO_2NH_2
TBAF	=	tetra-n-butylammonium fluoride
Th	=	2- or 3-thienyl
TFAA	=	trifluoroacetic acid anhydride
THF	=	tetrahydrofuran
Thi	=	thiophenediyl
TLC	=	thin layer chromatography
TMS-CN	=	trimethylsilyl cyanide
Tz	=	1H (or 2H)-tetrazol-5-yl
C_3H_5	=	allyl

Alkyl Group Abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

EXAMPLE 1

3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Step 1: 2-Bromo-1-(4-(methylsulfonyl)phenyl)ethanone

A solution of 197 g of 4-(methylthio)acetophenone (ref: *JACS, 1952, 74*, p. 5475) in 700 mL of MeOH and 3500 mL of CH_2Cl_2 was added 881 g of MMPP over a period of 30 min. After 3 h at room temperature the reaction mixture was filtered and the filtrate was washed with 2 L of saturated aqueous solution of $NaHCO_3$ and 1 L of brine. The aqueous phase was further extracted with 2 L of CH_2Cl_2. The combined extracts was dried over Na_2SO_4 concentrated to give 240 g of 4-(methylsulfonyl)acetophenone as a white solid.

To a cooled (-5 °C) solution of 174 g of 4-(methylsulfonyl)acetophenone in 2.5 L of $CHCl_3$ was added 20 mg of $AlCl_3$, followed by a solution of 40 mL of Br_2 in 300 mL $CHCl_3$. The reaction mixture was then treated with 1.5 L of water and the $CHCl_3$ was separated. The aqueous layer was extracted with 1 L of EtOAc. The combined extracts was dried over Na_2SO_4 and concentrated. The crude product was recystalized from 50/50 EtOAc/hexane to give 210 g of the title compound as a white solid.

Step 2:

To the product of Step 1 (216 mg) dissolved in acetonitrile (4 mL) was added Et_3N (0.26 mL), followed by 4-fluorophenylacetic acid (102 mg). After 1.5 h at room temperature 0.23 mL of DBU was added. The reaction mixture was stirred for another 45 min and then treated with 5 mL of 1 N HCl. The product was extracted with EtOAc, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (40% EtOAc in hexane) to yield 150 mg of the title compound as a solid.

^1H NMR (CD_3COCD_3) δ 3.15 (3H, s), 5.36 (3H, s), 7.18 (2H, J=8.9 Hz, t), 7.46 (2H, m), 7.7 (2H, J=8.65 Hz, d), 7.97 (2H, J=8.68, d).

EXAMPLE 2

3-(4-Fluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2*H*)-furanone

^{1}H NMR (CD_3COCD_3) δ 5.34 (2H, s), 6.67 (2H, bd), 7.18 (2H, m), 7.46 (2H, m), 7.61 (2H, m), 7.90 (2H, m).
M.P. 187-188°C (d).

EXAMPLE 3

5,5-Dimethyl-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Step 1: Methyl 2-trimethylsilyloxyisobutyrate

To a solution of 1.2 mL (10.4 mmol) of methyl 2-hydroxyisobutyrate in 50 mL of CH_2Cl_2 were added 1.2 g (17.6 mmol) of imidazole and 2.1 mL (16.6 mmol) of TMSCl. The mixture was stirred at r.t. for 1.5 h and quenched with 20 mL of H_2O. The organic layer was dried over $MgSO_4$, concentrated and passed through a short plug of silica gel eluted with 9:1 hexane/EtOAc. Evaporation of solvent afforded 1.27 g of the title compound as a colorless oil.
^{1}H NMR (CD_3COCD_3) δ 0.08 (9H, s), 1.38 (6H, s), 3.67 (3H, s).

Step 2: 2-Trimethylsilyloxy-4'-(methylthio)isobutyrophenone

A solution of 204 mg (1.0 mmol) of 4-bromothioanisole in 2.5 mL of THF was cooled to -78°C and treated with 0.42 mL of 2.5 M n-BuLi solution in hexane. After stirring at -78°C for 1 h, a solution of 380 mg (2.0 mmol) of methyl 2-trimethylsilyloxyisobutyrate in 2 mL of THF was added. The mixture was stirred at -78°C for 2 h and then quenched with NH_4OAc buffer. The product was extracted with EtOAc, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 19:1 hexane/EtOAc to give 95 mg of the title product.

^{1}H NMR (CD_3COCD_3) δ 0.05 (9H, s), 1.52 (6H, s), 2.53 (3H, s), 7.33 (2H, d), 8.12 (2H, d).

Step 3: 2-Hydroxy-4'-(methylthio)isobutyrophenone

To a solution of 40 mg (0.14 mmol) of 2-trimethylsilyloxy-4'-(methylthio)isobutyrophenone in 2 mL THF was added 0.2 mL of 1 M n-Bu_4NF in THF. The resulting mixture was stirred for 30 min and then quenched with 10 mL of NH_4OAc buffer. The product was extracted with EtOAc, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 4:1 hexane/EtOAc to give 25 mg of the title product.
^{1}H NMR (CD_3COCD_3) δ 1.50 (6H, s), 2.54 (3H, s), 4.68 (1H, s), 7.30 (2H, d), 8.15 (2H, d).

Step 4: 2-(4-Fluorophenylacetoxy)-4'-(methylthio)isobutyrophenone

To a solution of 72 mg (0.34 mmol) 2-hydroxy-4'-(methylthio)isobutyrophenone in 1.7 mL of CH_2Cl_2 were added 0.2 mL of pyridine and 140 mg (0.81 mmol) of 4-fluorophenylacetyl chloride. The mixture was stirred at r.t. overnight and then quenched with NH_4OAc buffer. The product was extracted with EtOAc, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography eluting with 8:1 hexane/EtOAc to give 95 mg of the title product.
^{1}H NMR (CD_3COCD_3) δ 1.62 (3H, s), 1.67 (3H, s), 2.48 (3H, s), 3.79 (2H, s), 7.0-7.3 (6H, m), 7.78 (2H, d).

Step 5: 5,5-Dimethyl-3-(4-fluorophenyl-4-(4-(methylthio)phenyl)-2-(5*H*)-furanone

To a solution of 95 mg of 2-(4-fluorophenylacetoxy)-4'-(methylthio)isobutyrophenone in 4 mL of CH_2Cl_2 was added 0.2 mL of DBU. The mixture was stirred for 4 h and diluted with NH_4OAc buffer. The product was extracted with EtOAc, dried over $MgSO_4$ and

concentrated. The residue was purified by flash chromatography, eluting with 20:1 toluene/EtOAc to give 75 mg of the title product. ^{1}H NMR (CD_3COCD_3) δ 1.58 (6H, s), 2.50 (3H, s), 7.03 (2H, dd), 7.25-7.35 (4H, m), 7.41 (2H, dd).

Step 6: 5,5-Dimethyl-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)-phenyl)-2-(*5H*)-furanone

To a solution of 81 mg of 5,5-dimethyl-3-(4-fluorophenyl)-4-(4-(methylthio)phenyl)-2-(*5H*)-furanone in 1.8 mL of CH_2Cl_2 and 0.2 mL of MeOH was added 250 mg of MPPM. The reaction mixture was stirred at room temperature for 1 h and then quenched with aqueous $NaHCO_3$. The product was extracted with EtOAc, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography eluting with 1:1 hexane/EtOAc to give 73 mg of the title product.
^{1}H NMR (CD_3COCD_3) δ 1.62 (6H, s), 3.15 (3H, s), 7.02 (2H, dd), 7.40 (2H, dd), 7.65 (2H, d), 8.03 (2H, d).

EXAMPLE 4

3-(2,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis calculated for $C_{17}H_{12}F_2O_4S$
C, 58.28; H, 3.45; S, 9.15
Found: C, 58.27; H, 3.50; S, 9.27

EXAMPLE 5

3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

To a solution of 3,4-difluorophenylacetic acid (ALDRICH CHEMICAL) (10 g) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (Example 9, Step 1) (17.3 g) in acetonitrile (200 mL) at room temperature was added slowly Et_3N (20.2 mL). After 1 h at r.t., the mixture was cooled in an ice bath and

treated with 17.4 mL of DBU. After 2 h at 0°C, the mixture was treated with 200 mL of 1 N HCl and the product was extracted with EtOAc, dried over Na_2SO_4 and concentrated. The residue was applied on top of a silica gel plug (sintered glass funnel) eluted with 75% EtOAc/hexane, giving, after evaporation of the solvent and swishing in EtOAC, 10 g of the title compound.

Analysis calculated for $C_{17}H_{12}F_2O_4S$
C, 58.28; H, 3.45; S, 9.15
Found: C, 58.02; H, 3.51; S, 9.35

EXAMPLE 6

3-(2,6-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}F_2O_4S$
C, 58.28; H, 3.45; S, 9.15
Found: C, 58.18; H, 3.50; S, 9.44

EXAMPLE 7

3-(2,5-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}F_2O_4S$
C, 58.28; H, 3.45; S, 9.15
Found: C, 58.89; H, 3.51; S, 9.11

EXAMPLE 8

3-(3,5-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}F_2O_4S$
C, 58.28; H, 3.45; S, 9.15
Found: C, 58.27; H, 3.62; S, 9.32

EXAMPLE 9

3-(4-Bromophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{13}BrO_4S$
C, 51.94; H, 3.33; S, 8.16
Found: C, 51.76; H, 3.42; S, 8.21

EXAMPLE 10

3-(4-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (2H, d), 7.49 (2H, d), 7.35 (4H, m), 5.16 (2H, s), 3.06 (3H, s)

EXAMPLE 11

3-(4-Methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{18}H_{16}O_5S$
C, 62.78 H, 4.68; S, 9.31
Found: C, 62.75; H, 4.72; S, 9.39

EXAMPLE 12

3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

To a solution of phenylacetic acid (27.4 g, 201 mmol) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (Example 1, Step 1) (60 g, 216 mmol, 1.075 eq.) in acetonitrile (630 mL) at 25°C was added slowly Et_3N (30.8 mL, 1.1 eq.). The mixture was stirred for 20 min. at room temperature and then cooled in an ice bath. DBU (60.1 mL, 3 eq.) was slowly added. After stirring for 20 min. in the ice bath, the reaction was complete and the mixture was acidified with 1 N HCl (color changes from dark brown to yellow). Then 2.4 L of ice and H_2O were added, stirred for a few minutes, then the precipitate was filtered and rinsed with H_2O (giving 64 g of crude wet product). The solid was dissolved in 750 mL of CH_2Cl_2 (dried over $MgSO_4$, filtered) and 300 g of silica gel was added. The solvent was evaporated to near dryness (silica gel a bit sticky) and the residue was applied on top of a silica gel plug (sintered glass funnel), eluted with 10% EtOAc/CH_2Cl_2, giving, after evaporation of the solvent and swishing in EtOAC, 36.6 g (58%) of the title compound.

Analysis	calculated for $C_{17}H_{14}O_4S$
	C, 64.95; H, 4.49; S, 10.20
Found:	C, 64.63; H, 4.65; S, 10.44

EXAMPLE 12A

3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Into a 20 mL glass ampule are added 1 g of 2-(4-(methylsulfonyl)phenyl)phenylacetylene, 20 mg of $Rh_4(CO)_{12}$, 1.5 g of Et_3N, 10 mL of THF, 1 mL of H_2O under a nitrogen atmosphere, and the ampule is placed in a 100-mL stainless steel autoclave. The reaction system is flushed three times with CO then charged at r.t. to an initial CO pressure of 100 atm. The reaction is carried at 100 C for 5 h. The solution is then diluted with 50 mL f benzene and washed with brine

and 1 N HCl. The benzene solution is dried over Na_2SO_4, and concentrated. The crude products are separated by column chromatography on silica gel, eluting with 2:1 EtOAc/hexane to give the title compound and its regioisomer, 4-(phenyl)-3-(4-(methylsolfonyl)-phenyl-2-(5H)-furanone.

EXAMPLE 12B

3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Step 1: 2-trimethylsilyloxy-4-(4-(methylthio)phenyl)-3,4-dihydrofuran

To a solution of 3.86 g (19 mmol) of 4-bromothioanisole in 90 mL of Et_2O cooled at -78°C, is added 22 mL of 1.7 M solution of t-BuLi in pentane (38 mmol) dropwise. The reaction mixture is stirred for 15 min at -78°C and 3.8 g of CuI is added and the reaction mixture is allowed to warm to -40 °C over a period of 30 min. A solution of 1.7 g of 2(5*H*)-furanone in 10 mL of THF is added. After stirring for 1 h, 2 mL of freshly distilled TMSCl is added dropwise. The reaction mixture is then treated with 2 mL of Et_3N and 50 mL of sat. $NaHCO_3$, and extracted with 100 mL of Et_2O . The Et_2O layer is dried over Na_2SO_4 and concentrated to give the crude title compound which is used for the next step without further purification.

Step 2: 4-(4-(methylthio)phenyl)-2-(5*H*)-furanone

To a solution of 4 g of $Pd(OAc)_2$ in 100 mL of acetonitrile is added dropwise the crude product from Step 1(5 g) under nitrogen at r.t. After 10 h at r.t., the mixture is condensed under reduced pressure and the residue is purified by flash chromatography on silica gel eluted with 2:1 hexane/EtOAc to give the title compound.

Step 3: 3-iodo-4-(4-(methylthio)phenyl)-2-(5*H*)-furanone

To a solution of 3 g of the product of Step 2 in 30 ml of pyridine is added 8.7 g of I_2. The mixture is stirred for 24 h and then

diluted with 200 mL of Et_2O, washed with 100 mL of 5 N HCl and 50 mL of 5 N $Na_2S_2O_3$. The Et_2O layer is dried over Na_2SO_4 and concentrated to give the title compound.

Step 4: 3-(Phenyl)-4-(4-(methylthio)phenyl)-2-(5*H*)-furanone

A mixture of 4 g of the product of Step 3, 3.7 g of $PhB(OH)_2$, 0.4 g of Ph_3As, 0.4 g of $PdCl_2(PhCN)_2$ in 100 mL of benzene and 15 mL of 2 N NaOH is refluxed for 6 h. Ether (200 mL) is then added and the mixture is washed with 100 mL of saturated $NaHCO_3$. The organic layer is dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography on silica gel eluted with 4:1 hexane/EtOAc to give the title compound.

Step 5: 3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

To a solution of 3 g of the product of Step 4 in 80 mL of 10:1 CH_2Cl_2/MeOH is added 5.5 g of MPPM. The reaction mixture is stirred at room temperature for 2 h and then diluted with 100 mL of 1:1 hexane/EtOAc. After filtration and concentration, the residue is purified by flash chromatography eluted with 2:1 EtOAc/hexane to give the title product.

EXAMPLE 13

3-(2-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{13}ClO_4S$

C, 58.54; H, 3.76; S, 9.19

Found: C, 58.59; H, 3.80; S, 9.37

EXAMPLE 14

3-(2-Bromo-4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis calculated for $C_{17}H_{12}BrFO_4S$
C, 49.75; H, 2.93
Found: C, 49.75; H, 3.01

EXAMPLE 15

3-(2-Bromo-4-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

^1H NMR (300 MHz, acetone-d_6) δ 7.95 (2H, d), 7.85 (1H, d), 7.63 (2H, dd), 7.55 (1H, dd), 7.45 (1H, d), 5.50 (2H, s), 3.15 (3H, s)

EXAMPLE 16

3-(4-Chloro-2-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

^1H NMR (300 MHz, acetone-d_6) δ 8.0 (2H, d), 7.70 (2H, d), 7.50-7.30 (3H, m), 5.35 (2h, s), 3.15 (3H, s)

EXAMPLE 17

3-(3-Bromo-4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis calculated for $C_{17}H_{12}BrFO_4S$
C, 49.75; H, 2.93
Found: C, 49.44; H, 2.98

EXAMPLE 18

3-(3-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{13}ClO_4S$
C, 58.54; H, 3.76
Found: C, 58.29; H, 3.76

EXAMPLE 19

3-(2-Chloro-4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}ClFO_4S$
C, 55.67; H, 3.30
Found: C, 55.67; H, 3.26

EXAMPLE 20

3-(2,4-Dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}Cl_2O_4S$
C, 53.28; H, 3.16; S, 8.37
Found: C, 52.89; H, 3.23; S, 8.58

EXAMPLE 21

3-(3,4-Dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}Cl_2O_4S$
C, 53.28; H, 3.16; S, 8.37
Found: C, 53.07; H, 3.32; S, 8.51

EXAMPLE 22

3-(2,6-Dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis calculated for $C_{17}H_{12}Cl_2O_4S$
C, 53.28; H, 3.16; S, 8.37
Found: C, 52.99; H, 3.22; S, 8.54

EXAMPLE 23

3-(3-Chloro-4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

^{1}H NMR (300 MHz, acetone-d_6) δ 8.0 (2H, d), 7.70 (2H, d), 7.60 (1H, d), 7.25-7.40 (2H, m), 5.35 (2H, s), 3.15 (3H, s)

EXAMPLE 24

3-(4-Trifluoromethylphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

^{1}H NMR (CD_3COCD_3) δ 8.10 (2H, d), 7.82-7.93 (4H, m), 7.75 (2H, d), 5.55 (2H, s), 3.30 (3H, s)

EXAMPLE 25

3-(3-Fluoro-4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis calculated for $C_{18}H_{15}FO_5S$
C, 59.66; H, 4.17
Found: C, 59.92; H, 4.37

EXAMPLE 26

3-(3-Chloro-4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis calculated for $C_{18}H_{15}ClO_5S$
C, 57.07; H, 3.99
Found: C, 57.29; H, 4.15

EXAMPLE 27

3-(3-Bromo-4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis calculated for $C_{18}H_{15}BrO_5S$
C, 51.08; H, 3.57
Found: C, 51.38; H, 3.62

EXAMPLE 28

3-(2-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis calculated for $C_{17}H_{13}FO_4S$
C, 61.44; H, 3.94
Found: C, 61.13; H, 3.85

EXAMPLE 29

3-(4-Methylthiophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

^1H NMR (300 MHz, acetone-d_6) δ 8.0 (2H, d), 7.70 (2H, d), 7.35 (2H, d), 7.25 (2H, d), 5.35 (2H, s), 3.15 (3H, s), 2.55 (3H, s)

EXAMPLE 30

3-(3-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (2H, d), 7.49 (2H, d), 7.35 (1H, m), 7.12 (3H, m), 5.18 (2H, s), 3.06 (3H, s)

EXAMPLE 31

3-(2-Chloro-6-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

^{1}H NMR (300 MHz, acetone-d6) δ 8.0 (2H, d), 7.70 (2H, d), 7.55-7.65 (1H, m), 7.40 (1H, d), 7.30 (1H, m), 5.60 (2H, s), 3.15 (3H, s)

EXAMPLE 32

3-(3-Bromo-4-methylphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis	calculated for $C_{18}H_{15}BrO_4S$
	C, 53.08; H, 3.71
Found:	C, 53.06; H, 3.83

EXAMPLE 33

3-(4-Bromo-2-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis	calculated for $C_{17}H_{12}BrFO_4S$
	C, 49.65; H, 2.94
Found:	C, 49.76; H, 3.00

EXAMPLE 34

3-(3,4-Dibromophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

^{1}H NMR (300 MHz, acetone-d6) δ 8.0 (2H, d), 7.80 (1H, d), 7.75 (3H, m), 7.25 (1H, d), 5.35 (2H, s), 3.15 (sH, s)

EXAMPLE 35

3-(4-Chloro-3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}ClFO_4S$
C, 55.67; H, 3.30
Found: C, 55.45; H, 3.30

EXAMPLE 36

3-(4-Bromo-3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}BrFO_4S$
C, 49.66; H, 2.94; S, 7.80
Found: C, 49.79; H, 3.01; S, 7.51

EXAMPLE 37

3-(4-Bromo-2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}BrClO_4S$
C, 47.74; H, 2.83; S, 7.50
Found: C, 47.92; H, 2.84; S, 7.42

EXAMPLE 38

3-(2-Naphthyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{21}H_{16}O_4S$
C, 69.22; H, 4.43
Found: C, 69.22; H, 4.46

EXAMPLE 39

3-(7-Quinolinyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{20}H_{15}NO_4S$
C, 65.74; H, 4.14; N, 3.83
Found: C, 65.34; H, 4.40; N, 3.80
M.S. (DCI, CH_4) calculated for M^+, 365
Found for M^++1, 366

EXAMPLE 40

3-(3,4-Dichlorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2*H*)-furanone

^1H NMR (400 MHz, CD_3COCD_3) δ 7.92 (2H, dd), 7,64 (3H, dm), 7.60 (1H, dd), 7.32 (1H, dd), 6.70 (1H, bs), 5.38 (2H, s)

EXAMPLE 41

3-(3,4-Difluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2*H*)-furanone

^1H NMR (400 MHz, CD_3COCD_3) δ 7.92 (2H, dd), 7,64 (2H, dd), 7.30-7.45 (2H, m), 7.22 (1H, m), 6.68 (2H, bs), 5.37 (2H, s)

EXAMPLE 42

3-(3-Chloro-4-methoxyphenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2*H*)-furanone

Analysis calculated for $C_{17}H_{14}ClNO_5S$
C, 53.76; H, 3.72, N, 3.69
Found: C, 53.32; H, 3.84, N, 3.59
M.S. (DCI, CH_4) calculated for M^+, 379
Found for M^++1, 380

EXAMPLE 43

3-(3-Bromo-4-methoxyphenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2*H*)-furanone

Analysis calculated for $C_{17}H_{14}BrNO_5S$
C, 48.13; H, 3.33, N, 3.30
Found: C, 48.26; H, 3.40, N, 3.28
M.S. (DCI, CH_4) calculated for M^+, 423
Found for M^++1, 424

Assays for Determining Biological Activity

The compound of the instant invention can be evaluated for efficacy by use of one or more of the following assays. As appreciated by those of skill in the art, the efficacy of a compound within the scope of the invention may be determined by statistical comparison of results achieved in the presence of that compound to that which is achieved in it's absence. Alternative may also be utilized

BONE RESORPTION (PIT) ASSAY

When osteoclasts engage in bone resorption, they will literally cause the formation of pits in the surface of bone that they are acting upon. Therefore, when testing compounds for their ability to

inhibit osteoclasts, it is useful to measure the ability of osteoclasts to excavate these resportion pits when the inhibiting compound is present.

Preparation of bone slices:

Bone slices (20 µm) are obtained by cutting 5 mm sections of bovine bone cylinders taken from bovine femur diaphysis using a low-speed diamond saw (Isomet, Buehler, Ltd., Lake Bluff, IL) following by the method of Arnett and Dempster, Endocrinology 120:602-608, 1987.

Slices are cleaned by ultrasonication, 3X in distilled water at 15 mins each. The slices are then rinsed in distilled water and placed in a 96-well plates. The plates are then placed in a tissue culture hood under uv light to sterilize and dry the bone slices. Prior to incubation with osteoclasts, bone slices were rehydrated in 0.1 ml complete medium 199 with 1% antimycotic/antibiotics (GIBCO, New York) and 10% fetal calf serum for 60 min.

Preparation of osteoclasts:

Rat long bones (tibiae, femora, humeri) are obtained from newborn rats (1-3 days old), cleaned of adherent tissue and minced in ice with scalpel blades in 3 ml Medium 199. The resulting suspension was gently pipetted 120 times with a wide-bore pipet and adjusted such that 750 µl of media is utilized for a preparation from one rat. The cell suspension is then filtered through a 100 µm nylon cell strainer (Falcon). The resulting suspension is then aliquoted at 100 µm/well. Finally, 22 µl of a 10X concentration of test drug is added to each well.

Incubation, staining and quantitation of pits:

Osteoclasts and bone slices are incubated for 24 hrs, the bone slices are washed 2X in PBS, then fixed with 2.5% glutaraldehyde/0.1 M cacodylate (100 µl/well) for at least 20 mins. The bone slices are then washed for 2X in PBS and sonicated for 2 min in 0.25 M NH_4OH at 100 µl/well in order to strip the cells from the lacunae. The bones are subsequently sonicated twice more in distilled

water, 15 min each. The bone slices are stained in the wells with 1% toluidine blue/1% sodium borate for 5-7 min. The bone slices are dried and the number of pits are counted by epi-fluorescence.

OCFORM ASSAY

Osteoblast-like cells (1.8 cells), originally derived from mouse calvaria, are plated in CORNING 24 well tissue culture plates in α MEM medium containing ribo- and deoxyribonucleosides, 10% fetal bovine serum and penicillin-streptomycin. Cells are seeded at 40,000/well in the morning. In the afternoon, bone marrow cells are prepared from six week old male Balb/C mice as follows:

Mice are sacrificed, tibiae removed and placed in the above medium. The ends are cut off and the marrow is flushed out of the cavity into a tube with a 1 mL syringe with a 27.5 gauge needle. The marrow is suspended by pipetting up and down with a glass pasteur pipette. The suspension is passed through two layers of approximately 400 μm mesh stainless steel cloth. The resulting suspension is centrifuged at 350 x g for seven minutes. The pellet is resuspended, and a sample is diluted in 2% HOAC to lyse the red cells. The remaining cells are counted in a hemocytometer. The cells are pelleted and resuspended at 1 x 10^6 cells/mL. 50 μL is added to each well to yield 50,000 cells/well and 1,25-dihydroxy-vitamin D3(D3) is added to each well to a final concentration of 10 nM. The cultures are incubated at 37°C in a humidified, 5% CO_2 atmosphere. After 48 h, the medium is changed. 72 h after the addition of bone marrow, test compounds are added with fresh medium containing D3 to triplicate wells. Compounds are added again after 48 h with fresh medium containing D3. After an additional 24 h the medium is removed, cells are fixed with 10% formaldehyde in phosphate buffered saline for 10 minutes at r.t., followed by a 1-2 minute treatment with EtOH:acetone (1:1) and air dried. The cells are then stained for tartrate resistant acid phosphatase as follows:

The cells are stained for 10-15 minutes at room temperature with 50 mM acetate buffer, pH 5.0 containing 30 mM sodium tartrate, 0.3 mg/mL Fast Red Violet LB Salt and 0.1 mg/mL Naphthol AS -MX phosphate. After staining, the plates are washed

extensively with deonized water and air dried. The number of multinucleated, positively staining cells are counted in each well.

While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for severity of bone disorders caused by resorption, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A method of inhibiting bone resorption in a patient in need of such inhibition comprising:
administration of a non-toxic therapeutically effective amount of a selective cyclooxygenase-2 inhibitor.

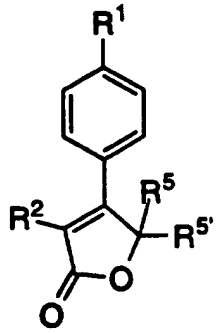
2. A method of preventing, retarding, halting or reversing loss of bone mass in a patient in need of such prevention comprising:
administration of a non-toxic therapeutically effective amount of a selective cyclooxygenase-2 inhibitor.

3. A method of reducing fractures in a patient in need of such reduction comprising:
administration of a non-toxic therapeutically effective amount of a selective cyclooxygenase-2 inhibitor.

4. A method of preventing, retarding, halting or reversing osteoporosis in a patient in need of such prevention comprising:
administration of a non-toxic therapeutically effective amount of a selective cyclooxygenase-2 inhibitor.

5. A method of maintaining bone density in a patient in need of such maintenance comprising:
administration of a non-toxic therapeutically effective amount of a selective cyclooxygenase-2 inhibitor.

6. A method according to Claim 1 wherein the inhibitor is a compound of Formula Ia



Ia

or pharmaceutically acceptable salts thereof wherein:

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)NHCH_3$,
(e) $S(O)NHNH_2$, and
(f) $S(O)NHNHC(O)CF_3$;

R^2 is selected from the group consisting of

(a) C_{1-6}alkyl,
(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
(c) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,
(9) $-CO_2H$,

(10) -CO_2-C_{1-4}alkyl,
(11) -$C(R^3)(R^4)$-OH,
(12) -$C(R^3)(R^4)$-O-C_{1-4}alkyl, and
(13) -C_{1-6}alkyl-CO_2-R^3;

(d) heteroaryl
(e) benzoheteroaryl

R^3, R^4, R^5 and $R^{5'}$ are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-6}alkyl.

7. A method according to Claim 6 wherein

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$, and
(b) $S(O)_2NH_2$,

R^2 is

mono or di-substituted phenyl wherein the substituents are selected from the group consisting of

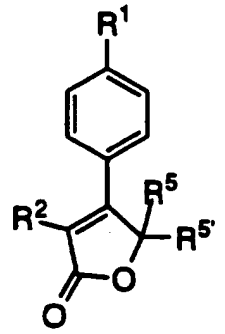
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo; and

R^5 and $R^{5'}$ are each hydrogen.

8. A method according to Claim 7 wherein the compound of Formula Ia is

3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone, or a pharmaceutically acceptable salt thereof.

9. A method according to Claim 2 wherein the inhibitor is a compound of Formula Ia



Ia

or pharmaceutically acceptable salts thereof wherein:

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)NHCH_3$,
(e) $S(O)NHNH_2$, and
(f) $S(O)NHNHC(O)CF_3$;

R^2 is selected from the group consisting of

(a) C_{1-6}alkyl,
(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
(c) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl;

(8) N_3,
(9) $-CO_2H$,
(10) $-CO_2-C_{1-4}$alkyl,
(11) $-C(R^3)(R^4)-OH$,
(12) $-C(R^3)(R^4)-O-C_{1-4}$alkyl, and
(13) $-C_{1-6}$alkyl$-CO_2-R^3$;

(d) heteroaryl
(e) benzoheteroaryl

R^3, R^4, R^5 and $R^{5'}$ are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-6}alkyl.

10. A method according to Claim 9 wherein R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$, and
(b) $S(O)_2NH_2$,

R^2 is

mono or di-substituted phenyl wherein the substituents are selected from the group consisting of

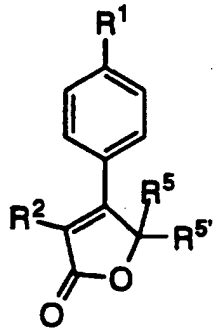
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo; and

R^5 and $R^{5'}$ are each hydrogen.

11. A method according to Claim 10 wherein the compound of Formula Ia is

3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone, 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone, or a pharmaceutically acceptable salt thereof.

12. A method according to Claim 3 wherein the inhibitor is a compound of Formula Ia



Ia

or pharmaceutically acceptable salts thereof wherein:

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)NHCH_3$,
(e) $S(O)NHNH_2$, and
(f) $S(O)NHNHC(O)CF_3$;

R^2 is selected from the group consisting of

(a) C_{1-6}alkyl,
(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
(c) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,

(8) N_3,
(9) $-CO_2H$,
(10) $-CO_2-C_{1-4}$alkyl,
(11) $-C(R^3)(R^4)-OH$,
(12) $-C(R^3)(R^4)-O-C_{1-4}$alkyl, and
(13) $-C_{1-6}$alkyl$-CO_2-R^3$;
(d) heteroaryl
(e) benzoheteroaryl

R^3, R^4, R^5 and $R^{5'}$ are each independently selected from the group consisting of
(a) hydrogen,
(b) C_{1-6}alkyl.

13. A method according to Claim 12 wherein R^1 is selected from the group consisting of
(a) $S(O)_2CH_3$, and
(b) $S(O)_2NH_2$,

R^2 is

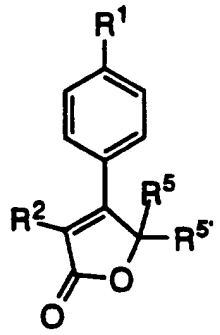
mono or di-substituted phenyl wherein the substituents are selected from the group consisting of
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo; and

R^5 and $R^{5'}$ are each hydrogen.

14. A method according to Claim 13 wherein the compound of Formula Ia is

3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone, or a pharmaceutically acceptable salt thereof.

15. A method according to Claim 4 wherein the inhibitor is a compound of Formula Ia



Ia

or pharmaceutically acceptable salts thereof wherein:

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)NHCH_3$,
(e) $S(O)NHNH_2$, and
(f) $S(O)NHNHC(O)CF_3$;

R^2 is selected from the group consisting of

(a) C_{1-6}alkyl,
(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
(c) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,

(8) N_3,
(9) $-CO_2H$,
(10) $-CO_2-C_{1-4}alkyl$,
(11) $-C(R^3)(R^4)-OH$,
(12) $-C(R^3)(R^4)-O-C_{1-4}alkyl$, and
(13) $-C_{1-6}alkyl-CO_2-R^3$;

(d) heteroaryl
(e) benzoheteroaryl

R^3, R^4, R^5 and $R^{5'}$ are each independently selected from the group consisting of

(a) hydrogen,
(b) $C_{1-6}alkyl$.

16. A method according to Claim 15 wherein R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$, and
(b) $S(O)_2NH_2$,

R^2 is

mono or di-substituted phenyl wherein the substituents are selected from the group consisting of

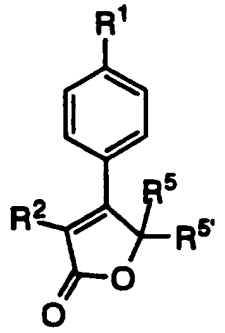
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo; and

R^5 and $R^{5'}$ are each hydrogen.

17. A method according to Claim 16 wherein the compound of Formula Ia is

3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone, or a pharmaceutically acceptable salt thereof.

18. A method according to Claim 5 wherein the inhibitor is a compound of Formula Ia



Ia

or pharmaceutically acceptable salts thereof wherein:

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)NHCH_3$,
(e) $S(O)NHNH_2$, and
(f) $S(O)NHNHC(O)CF_3$;

R^2 is selected from the group consisting of

(a) C_{1-6}alkyl,
(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
(c) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl;

(8) N_3,
(9) $-CO_2H$,
(10) $-CO_2-C_{1-4}$alkyl,
(11) $-C(R^3)(R^4)-OH$,
(12) $-C(R^3)(R^4)-O-C_{1-4}$alkyl, and
(13) $-C_{1-6}$alkyl$-CO_2-R^3$;
(d) heteroaryl
(e) benzoheteroaryl

R^3, R^4, R^5 and $R^{5'}$ are each independently selected from the group consisting of
(a) hydrogen,
(b) C_{1-6}alkyl.

19. A method according to Claim 16 wherein R^1 is selected from the group consisting of
(a) $S(O)_2CH_3$, and
(b) $S(O)_2NH_2$,

R^2 is

mono or di-substituted phenyl wherein the substituents are selected from the group consisting of
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo; and

R^5 and $R^{5'}$ are each hydrogen.

20. A method according to Claim 19 wherein the compound of Formula Ia is

3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone, or a pharmaceutically acceptable salt thereof.

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Patents Act 1977 Examiner's report to the Comptroller under Section 17 (The Search rep rt)	Application number GB 9520615.7
Relevant Technical Fields (i) UK Cl (Ed.N) A5B (BHA, BJA, BJB) (ii) Int Cl (Ed.6) A61K	Search Examiner DR J HOULIHAN Date of completion of Search 31 JANUARY 1996
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE: CAS ONLINE, DIALOG/MEDICINE, WPI	Documents considered relevant following a search in respect of Claims :- 1-20

Categories of documents

X:	Document indicating lack of novelty or of inventive step.	**P:**	Document published on or after the declared priority date but before the filing date of the present application.
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Category	Identity of document and relevant passages		Relevant to claim(s)
P,X	GB 2283745 A	(MERCK) page 2 lines 28-33; page 7 lines 26-34; Claim 7	1-5
P,X	WO 95/21817 A1	(SEARLE & CO) page 2 lines 4-9; page 4 line 6 - page 5 line 2; page 137 lines 13-26; Claims 36-51	1-5
P,X	WO 94/26731 A1	(MERCK) page 2 lines 10-31; page 6 lines 23-28; Claims 17, 19 and 20	1-5
X	WO 94/15932 A1	(SEARLE) page 2 lines 24-29; page 7 line 11 - page 8 line 4; page 27 lines 13-24; page 72 lines 23-35; page 74 lines 12-32; Claims 16-34	1-5
X	WO 94/13635 A1	(MERCK) page 12 line 18 - page 14 line 13; page 16 lines 8-32; Claims; Claims 22, 25 and 29	1-5
X	European J. Clin. Pharmacol. Vol. 47(1) 1994. Lemmel E M Suppl. A52 See Abstract		1-5

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